IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No. 5,888,510

Issued: March 30, 1999

Inventors: Tadamitsu KISHIMOTO et al.

Applicants: Chugai Seiyaku Kabushiki Kaisha
Tadamitsu Kishimoto

Product: Actemra® (tocilizumab), humanized anti-human IL-6R monoclonal antibody

APPLICATION FOR PATENT TERM EXTENSION UNDER 35 U.S.C. §156

Mail Stop: Hatch Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir or Madam:

Applicants Chugai Seiyaku Kabushiki Kaisha ("Chugai") and Tadamitsu Kishimoto ("Kishimoto") (collectively, "Applicants") hereby apply for patent term extension of U.S. Patent No. 5,888,510 under 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

Applicants are the owners of U.S. Patent No. 5,888,510, by virtue of assignment of all rights of inventors Tadamitsu Kishimoto, Masahiko Mihara, Yoichiro Moriya, and Yoshiyuki Ohsugi to Chugai and Kishimoto, as recorded in the U.S. Patent and Trademark Office on April 7, 1997, Reel 08525, Frame 0517 (copy attached hereto as Exhibit 1).

This application is based on the approval by the United States Food and Drug Administration ("FDA") of a Biologics License Application (BLA # 125276/0) on January 8, 2010, for Actemra® (tocilizumab), a humanized monoclonal antibody that is an interleukin-6 receptor (IL-6R) inhibitor, for the treatment of adult patients with rheumatoid arthritis.

For convenience, the information contained in this application will be presented according to the format set forth in 37 C.F.R. § 1.740(a).

(1) A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product is a recombinant humanized anti-human Interleukin-6 Receptor (IL-6R) monoclonal antibody of the immunoglobulin IgG_1 subclass, formulated for intravenous (iv) infusion. The approved product has the trade name Actemra®, and established name of "tocilizumab."

Actemra® (tocilizumab) is an IgG1κ (gamma 1, kappa) antibody with a typical H_2L_2 structure. The amino acid sequence of the light chain is shown in Figure 1.

Figure 1: Amino Acid Sequence of the L Chain

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  1    DIQMTQSPSS LSASVGDRVT ITCRASQDIS SYLNWYQQKP GKAPKLLIYY  50
 51    TSRLHSGVPS RFSGSGSGTD FTFTISSLQP EDIATYYCQQ GNTLPYTFGQ 100
101    GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
151    DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
201    LSSPVTKSFN RGEC                                       214
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The amino acid sequence of the heavy chain is shown in Figure 2.

Figure 2: Amino Acid Sequence of the H Chain

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  1   pEVQLQESGPG LVRPSQTLSL TCTVSGYSIT SDHAWSWVRQ PPGRGLEWIG  50
 51    YISYSGITTY NPSLKSRVTM LRDTSKNQFS LRLSSVTAAD TAVYYCARSL 100
101    ARTTAMDYWG QGSLVTVSSA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
151    YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
201    ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
251    DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
301    TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
351    YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
401    DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPG   448
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(2) A Complete Identification Of The Federal Statute Including The Applicable Provision Of Law Under Which The Regulatory Review Occurred

Regulatory review of the approved product occurred under § 505(i) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(i) (*see also* 21 C.F.R. Part 312)

and § 351(a) of the Public Health Service Act ("PHSA"), 42 U.S.C. § 262(a) (*see also* 21 C.F.R. Part 314 and 601).

(3) **An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred**

The approved product, Actemra® (tocilizumab), received permission for commercial marketing on January 8, 2010, when the FDA approved BLA # 125276/0 for the treatment of adults with rheumatoid arthritis, under § 351(a) of the PHSA.

(4) **In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug And Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved**

The approved product contains only one active ingredient, tocilizumab. Tocilizumab (Actemra®) has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) **A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant To 37 C.F.R. § 1.720(F) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted**

The Application is being submitted within the sixty day period permitted under 37 C.F.R. § 1.720(f) .

The last day on which the application can be submitted is March 8, 2010, i.e., sixty days from the date (January 8, 2010) the approved product first received permission for commercial marketing or use under the PHSA.

(6) A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of The Inventor, The Patent Number, The Date Of Issue, And The Date Of Expiration.

The patent for which an extension is being sought is:

Inventors:	Tadamitsu Kishimoto, Masahiko Mihara, Yoichiro Moriya, and Yoshiyuki Ohsugi
Patent No:	U.S. Patent No. 5,888,510
Title:	Chronic Rheumatoid Arthritis Therapy Containing IL-6 Antagonist as Effective Component
Issue Date:	March 30, 1999
Current Expiration Date:	March 30, 2016 (17 years from March 30, 1999 issue date of U.S. Patent No. 5,888,510)

The '510 patent has not previously been extended.

(7) A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A copy of U.S. Patent No. 5,888,510 is attached hereto as Exhibit 2.

(8) A Copy Of Any Disclaimer, Certificate Of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In The Patent.

No disclaimers, certificates of correction, or reexamination certificates have been issued in the patent. Copies of the 4th and 8th year maintenance fee payment receipts is attached hereto as Exhibit 3.

(9) A Statement That The Patent Claims The Approved Product, Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which At Least One Such Patent Claim Reads On The Method Of Using The Approved Product

U.S. Patent No. 5,888,510 claims a method of using the approved product Actemra® (tocilizumab) to treat chronic rheumatoid arthritis or inhibit synovial cell growth. As provided above, Actemra® is an interleukin-6 antagonist, and an anti-human interleukin-6 receptor antibody in particular, and the claims of the '510 patent relate to the use of an interleukin-6 antagonist to inhibit synovial cell growth or treat chronic rheumatoid arthritis, respectively. Thus, Actemra® is an antibody that binds an interleukin-6 receptor and specifically, a human interleukin-6 receptor. Actemra® is a monoclonal antibody. Accordingly, applicable claims of the '510 patent for patent term extension which claim the approved product include claims 1-4 and 6-10:

1. A method for inhibiting synovial cell growth, comprising administering to a patient in need thereof a pharmaceutical composition comprising an interleukin-6 antagonist and a physiologically acceptable carrier.

2. The method according to claim 1, wherein the interleukin-6 antagonist is selected from the group consisting of an interleukin-6 antibody and an interleukin-6 receptor antibody.

3. The method according to claim 2, wherein the antagonist is a monoclonal antibody.

4. The method according to claim 1, wherein the patient is a human.

6. A method of treating chronic rheumatoid arthritis, comprising administering to a patient in need thereof a pharmaceutical composition comprising an antibody against an interleukin-6 receptor and a physiologically acceptable carrier.

7. The method according to claim 6, wherein the antibody suppresses abnormal growth of synovial cells.

8. The method according to claim 6, wherein the antibody is an antibody against a human interleukin-6 receptor.

9. The method according to claim 6, wherein the antibody is a monoclonal antibody.

10. The method according to claim 6, wherein the patient is a human.

For the reasons discussed below, applicants request a patent term extension regarding claims 1-4 and 6-10.

Actemra® (tocilizumab) is an interleukin-6 receptor antagonist (and specifically, an antibody that binds the interleukin-6 receptor) that is used to treat adult patients with moderately to severely active rheumatoid arthritis.

Rheumatoid arthritis is a chronic systemic disease primarily of the joints, marked by inflammatory changes in the synovial membranes and articular structures and by atrophy and rarefaction of the bones. The patients enrolled in the clinical studies for Actemra® have been diagnosed with active rheumatoid arthritis according to the American College of Rheumatology criteria. See Full Prescribing Information for Actemra®, section 14 (Exhibit 4). Actemra® is approved for use in treating "adult patients with moderately - to severely – active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies." See Full Prescribing Information for Actemra®, section 1. Thus, the claims above relating to treatment of chronic rheumatoid arthritis cover the approved product and indication.[1]

Additionally, the relationship between IL-6 and synovial cells, and the ability of an IL-6 receptor antibody to inhibit synovial cell growth is supported by data in the '510 patent. Indeed, the '510 patent demonstrates that an anti-IL-6 receptor antibody suppresses abnormal

[1] Applicant further notes that the Japanese Ministry of Health, Labour and Welfare originally required companies in Japan to reference "rheumatoid arthritis" with Japanese characters that literally translate into "chronic rheumatoid arthritis" at the time the application underlying the '510 patent was filed. Hence, the phrase "chronic rheumatoid arthritis" was translated at the time the national stage of the application underlying the '510 patent was filed in the US. Under the prior usage in Japan, the term "rheumatoid arthritis" was previously referred to as "Mansei Kansetsu Riumachi", which literally translates as "chronic rheumatoid arthritis." However, after 2009, the term "rheumatoid arthritis" in Japanese was changed from "Mansei Kansetsu Riumachi" to "Kansetsu Riumachi." Accordingly, "chronic rheumatoid arthritis" at the time of translating the US national stage application that issued as the '510 patent is the same indication as "rheumatoid arthritis." *See* Exhibit 5.

growth of synovial cells. *See*, Examples 1 and 2 of the '510 patent. Additionally, the Full Prescribing Information for Actemra®, Section 12.1 provides that "IL-6 is produced by synovial cells, leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis." Thus, the claims above relating to inhibition of synovial cells claim the approved product and its approved indication.

In conclusion, claims 1-4 and 6-10 are eligible for patent term extension.

(10) A Statement Beginning On A New Page Of The Relevant Dates And Information Pursuant To 35 U.S.C. 156(g) In Order To Enable The Secretary Of Health And Human Services To Determine The Applicable Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C. § 156(g) needed to enable the Secretary of Health and Human Services to determine the applicable regulatory review period for the Approved Product (a human biological product) are as follows:

(A) The effective date of the Investigational New Drug Application (IND) and the IND number:

IND Effective Date: November 4, 2004

BB IND Number: 11972

(B) The date on which a Biologic License Application (BLA) was initially submitted and the BLA number:

BLA Submission Date: November 19, 2007

BLA Number: 125276/0

(C) The date on which the BLA was approved:

BLA Approval Date: January 8, 2010

(11) **A Brief Description Beginning on a new Page of the Significant Activities Undertaken By The Marketing Applicant During the Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable to Such Activities**

Please see attached Exhibit 6 for this Description. Several significant dates are also summarized below. Applicants reserve the right to supplement the activity description in Exhibit 6 if further clarification is needed.

DATE	*DESCRIPTION OF ACTIVITIES*
October 5, 2004	*FDA confirmation of IND submission*
November 4, 2004	*IND effective date*
November 19, 2007	*BLA 125276/0 submitted to and received by FDA*
January 8, 2010	*FDA approves BLA 125276/0*

(12) A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of Extension Claimed, Including How The Length Of Extension Was Determined

In the opinion of Applicants, U.S. Patent No. 5,888,510 is eligible for a patent term extension.

The length of the patent term extension claimed is 1338 days, which is believed to extend the patent term to at least November 28, 2019.

The length of the patent term extension claimed was determined in accordance with 37 C.F.R. § 1.775, as the length of the regulatory review period for the Approved Product as defined in 37 C.F.R. § 1.775(c), reduced as appropriate pursuant to 37 C.F.R. § 1.775(d)(1) through (d)(6).

As defined in 37 C.F.R. § 1.775(c), the length of the regulatory review period for the Approved Product is the sum of (1) and (2) below:

> **(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act.**

This is the number of days in the period beginning on the date the IND became effective, November 4, 2004, and ending on the date the BLA was initially submitted, November 19, 2007, which is 1111 days.

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act and ending on the date such application was approved under such section.

This is the number of days in the period beginning on the date the BLA was initially submitted, November 19, 2007, and ending on the date the BLA was approved, January 8, 2010, which is 782 days.

The sum of (1) and (2) above is 1111 days plus 782 days, which is 1893 days. Thus, the length of the regulatory review period for the Approved Product is 1893 days.

In accordance with 37 C.F.R. § 1.775(d)(1), the length of the extension is initially determined as follows:

(i) Subtracting from the regulatory review period the number of days in periods (1) and (2) above which were on and before the date on which the patent issued.

The IND became effective on November 4, 2004, and the patent issued on March 30, 1999. The number of days in periods (1) and (2) above which were on and before the date the patent issued is zero days. Subtracting 0 days from the regulatory review period leaves 1893 days.

(ii) Subtracting from the regulatory review period the number of days in periods (1) and (2) above during which it is determined that applicant did not act with due diligence.

Applicants acted with due diligence during the entire regulatory review period. Thus, no deduction is required under this subsection.

(iii) Subtracting from the regulatory review period one-half the number of days in (1) above remaining after that period is reduced in accordance with (i) and (ii) above.

The number of days in period (1) is 1111 days. That number is reduced by 0 days, in accordance with (i) above. One half of 1111 days is 555 days. Subtracting 555 days from 1893 days leaves 1338 days.

Thus, in accordance with (d)(1), the length of the extension is

(1893 days) – (0 days) – (555 days) = 1338 days

In accordance with 37 C.F.R. § 1.775(d)(2), the length of the extension is further determined as follows:

(2) Adding the number of days determined in accordance with 37 C.F.R. § 1.775(d)(1) to the original term of the patent, as shortened by any terminal disclaimer.

The patent's term is set to expire March 30, 2016. (There are no applicable terminal disclaimers). The addition of 1338 days of Patent Term Extension to that term would extend the term to at least November 28, 2019.

In accordance with 37 C.F.R. § 1.775(d)(3), the length of the extension is further determined as follows:

(3) Adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act

The application was approved on January 8, 2010. Adding 14 years to that date results in a date of January 8, 2024.

In accordance with 37 C.F.R. § 1.775(d)(4), the length of the extension is further determined as follows:

(4) By comparing the dates determined in accordance with 37 C.F.R. § 1.775(d)(2) and (d)(3) above and selecting the earlier date.

The earlier date of the two dates determined above in accordance with 37 C.F.R. § 1.776(d)(2) and (d)(3), is November 28, 2019.

In accordance with 37 C.F.R. § 1.775(d)(5), the length of the extension is further determined as follows:

(5) If the original patent was issued after September 24, 1984, adding five years to the original expiration date and comparing that date to the date obtained in accordance with 37 C.F.R. § 1.775(d)(4) and selecting the earlier date.

The original term of the patent expires March 30, 2016. (There are no applicable terminal disclaimers.) Adding five years to March 30, 2016, results in a date of March 30, 2021.

The earlier of March 30, 2021, and the date determined above in accordance with 37 C.F.R. § 1.776(d)(4) is November 28, 2019.

The provisions of 37 C.F.R. § 1.775(d)(6) apply only to patents issued before September 24, 1984, and thus are not applicable here.

Thus, the patent should be extended 1338 days which is believed to extend the term to at least November 28, 2019.

(13) A Statement That The Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Or The Secretary Of Agriculture Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicants acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determinations of entitlement to the extension sought herein.

(14) The Prescribed Fee For Receiving And Acting Upon The Application For Extension

A credit card authorization form for the prescribed fee is submitted herewith. Authorization is given to charge Deposit Account 19-0741 any deficiency in fees.

(15) The Name, Address, And Telephone Number Of The Person To Whom Inquiries And Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Inquiries and correspondence relating to this Application should be directed to the registered practitioner authorized to act on behalf of the patent owner in connection with this Application:

Stephen B. Maebius
Foley & Lardner LLP
3000 K Street, N.W.
Washington, D.C. 20007-5143
Tel: 202-672-5300

(16) Certification Under 37 C.F.R. § 1.740(b)

Two additional copies of this Application and Exhibits are submitted herewith in accordance with 37 C.F.R. § 1.740(b).

The undersigned is a registered practitioner authorized to act on behalf of the patent owner in connection with this Application.

Respectfully submitted,

Date February 26, 2010

By _____

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264

FOLEY & LARDNER LLP
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EXHIBIT 1
ASSIGNMENT RECORDATION

53466/200
HCW

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DECEMBER 07, 1998

PTAS

100841903A

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CORRECTED NOTICE

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 04/07/1997 REEL/FRAME: 8525/0517
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:
KISHIMOTO, TADAMITSU DOC DATE: 03/28/1997

ASSIGNOR:
MIHARA, MASAHIKO DOC DATE: 03/28/1997

ASSIGNOR:
MORIYA, YOICHIRO DOC DATE: 03/28/1997

ASSIGNOR:
OHSUGI, YOSHIYUKI DOC DATE: 03/28/1997

ASSIGNEE:
CHUGAI SEIYAKU KABUSHIKI KAISHA
5-1, UKIMA 5-CHOME, KITA-KU
TOKYO, JAPAN 115

REVIEWED BY

INITIALS LE DATE 9/20/01

GRANTED

ASSIGNEE:
KISHIMOTO, TADAMITSU
3-5-31, NAKANO-CHO, TONDABAYASHI-SHI
OSAKA, JAPAN 584

SERIAL NUMBER: 08817084
PATENT NUMBER:

FILING DATE: 04/07/1997
ISSUE DATE:

LENELL MACKALL, PARALEGAL
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

U.S. ASSIGNMENT

IN CONSIDERATION of the sum of One Dollar ($1.00), and of other good and valuable consideration paid to the undersigned inventor(s) (hereinafter "ASSIGNOR") by

(Insert ASSIGNEE's Name(s) Address(es))

1) CHUGAI SEIYAKU KABUSHIKI KAISHA

5-1, Ukima 5-chome, Kita-ku, Tokyo 115 Japan

2) Tadamitsu Kishimoto

3-5-31, Nakano-cho, Tondabayashi-shi, Osaka 584 Japan

(hereinafter "ASSIGNEE"), the receipt of which is hereby acknowledged, the undersigned ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the entire and exclusive right, title and interest to the invention entitled

(Title of Invention)

CHRONIC RHEUMATOID ARTHRITIS THERAPY CONTAINING IL-6 ANTAGONIST AS EFFECTIVE COMPONENT

relating to International Patent Application PCT/JP 95 / 01144 and/or for which application for Letters Patent of the United States was executed on even date herewith or, if not so executed, was:

(Insert date of execution of application, if not concurrent)

(a) executed on _____ ;

(b) filed on _____, Serial No. ____/_____;

(_____) is hereby authorized to insert in (b) the specified data, when known.

and to said application and all Letters Patent(s) of the United States granted on said application and any continuation, division, renewal, substitute, reissue or reexamination application based thereon, for the full term or terms for which the said Letters Patent(s) may be granted and including any extensions thereof (collectively, hereinafter, "said application(s) and Letters Patent(s)").

The ASSIGNOR agree(s), when requested by said ASSIGNEE and without charge to but at the expense of said ASSIGNEE, to do all acts which the ASSIGNEE may deem necessary, desirable or expedient, for securing, maintaining and enforcing protection for said invention, including in the preparation and prosecution of said application(s) and the issuance of said Letters Patent(s), in any interference, reissue, reexamination, or public use proceeding, and in any litigation or other legal proceeding which may arise or be declared in relation to same, such acts to include but not be limited to executing all papers, including separate assignments and declarations, taking all rightful oaths, providing sworn testimony, and obtaining and producing evidence.

IN WITNESS WHEREOF, the undersigned inventor(s) has (have) affixed his/her/their signature(s).

(Signatures)

	(SIGNATURE)	(TYPE NAME)	(DATE)
1)	[signature]	Tadamitsu Kishimoto	March 28, 1997
2)	[signature]	Masahiko Mihara	March 28, 1997
3)	[signature]	Yoichiro Moriya	March 28, 1997
4)	[signature]	Yoshiyuki Ohsugi	March 28, 1997
5)			
6)			
7)			
8)			

EXHIBIT 2
US PATENT 5,888,510

US005888510A

United States Patent [19]

Kishimoto et al.

[11] Patent Number: 5,888,510

[45] Date of Patent: Mar. 30, 1999

[54] **CHRONIC RHEUMATOID ARTHRITIS THERAPY CONTAINING IL-6 ANTAGONIST AS EFFECTIVE COMPONENT**

[75] Inventors: **Tadamitsu Kishimoto**, Tondabayashi; **Masahiko Mihara**, Gotenba; **Yoichiro Moriya**, Gotenba; **Yoshiyuki Ohsugi**, Gotenba, all of Japan

[73] Assignees: **Chugai Seiyaku Kabushiki Kaisha**, Tokyo; **Tadamitsu Kishimoto**, Tondabayashi, both of Japan

[21] Appl. No.: **817,084**

[22] PCT Filed: **Jun. 7, 1995**

[86] PCT No.: **PCT/JP95/01144**

§ 371 Date: **Apr. 7, 1997**

§ 102(e) Date: **Apr. 7, 1997**

[87] PCT Pub. No.: **WO96/11020**

PCT Pub. Date: **Apr. 18, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 971,997, Feb. 21, 1997, which is a continuation of Ser. No. 268,520, Jun. 30, 1994, abandoned.

[30] **Foreign Application Priority Data**

Jul. 21, 1993 [JP] Japan 5-180303
Aug. 25, 1993 [JP] Japan 5-210570
Oct. 7, 1994 [JP] Japan 6-244035

[51] **Int. Cl.**[6] **A61K 39/395**; A01N 37/18; C07K 16/24; C07K 16/28

[52] **U.S. Cl.** **424/141.1**; 424/145.1; 424/810; 514/2; 530/388.23; 530/389.2

[58] **Field of Search** 424/145.1, 141.1, 424/810; 530/388.23, 389.2; 514/2

[56] **References Cited**

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Assistant Examiner—F. Pierre VanderVegt
Attorney, Agent, or Firm—Foley & Lardner

[57] **ABSTRACT**

Methods for inhibiting synovial cell growth and treating chronic rheumatoid arthritis are provided. The methods comprise administering a pharmaceutical composition comprising an interleukin-6 antagonist, such as an anti-IL-6 receptor antibody, and a physiologically acceptable carrier.

11 Claims, 6 Drawing Sheets

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Fig. 1

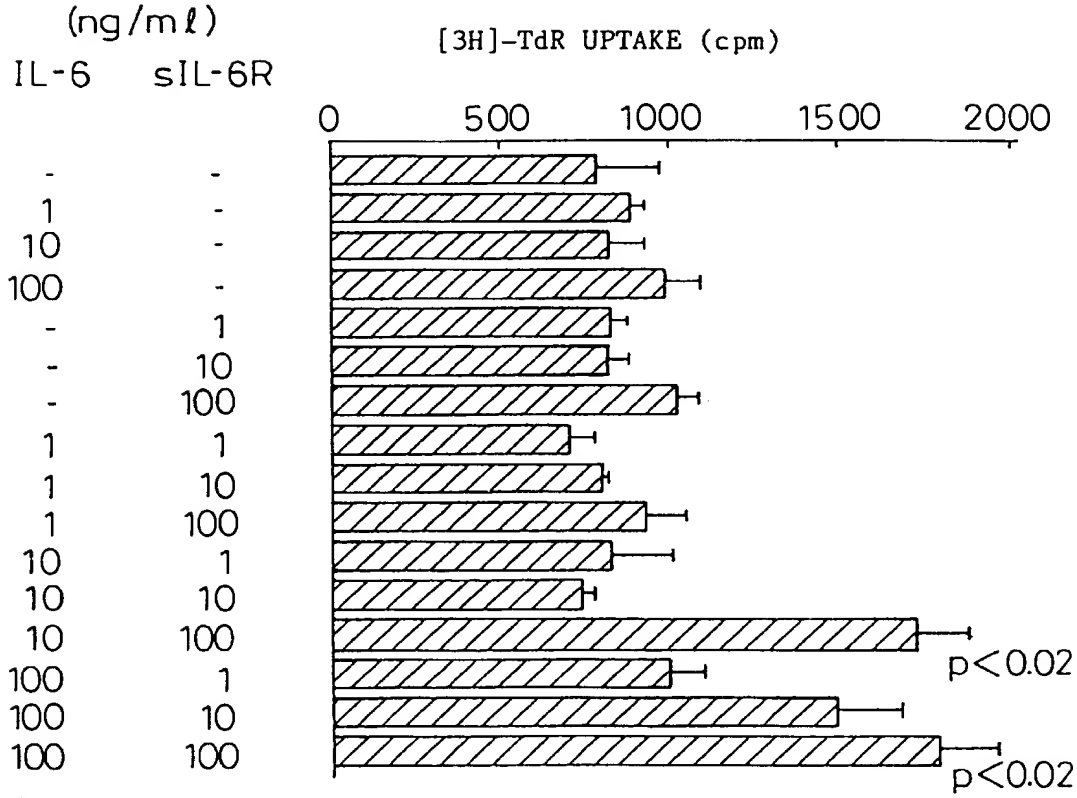

(ng/mℓ)
IL-6 sIL-6R
[3H]-TdR UPTAKE (cpm)
0 500 1000 1500 2000
- -
1 -
10 -
100 -
- 1
- 10
- 100
1 1
1 10
1 100
10 1
10 10
10 100
100 1
100 10
100 100
p<0.02
p<0.02

Fig. 2

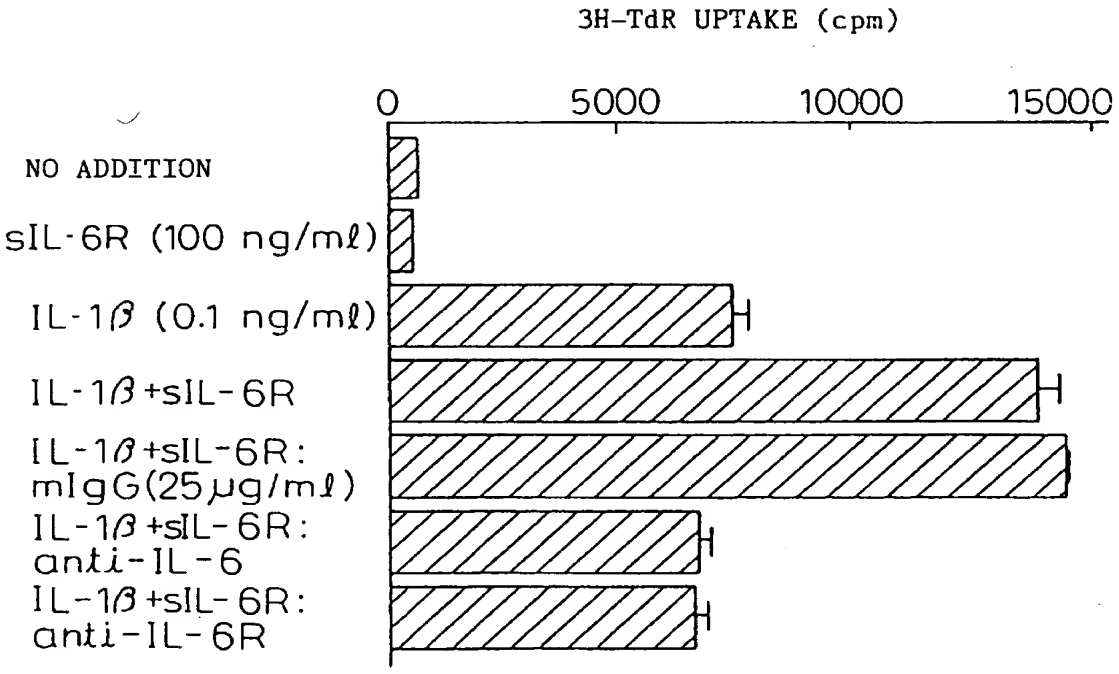

3H-TdR UPTAKE (cpm)
0
5000
10000
15000
NO ADDITION
sIL-6R (100 ng/mℓ)
IL-1β (0.1 ng/mℓ)
IL-1β+sIL-6R
IL-1β+sIL-6R: mIgG(25μg/mℓ)
IL-1β+sIL-6R: anti-IL-6
IL-1β+sIL-6R: anti-IL-6R

Fig. 3

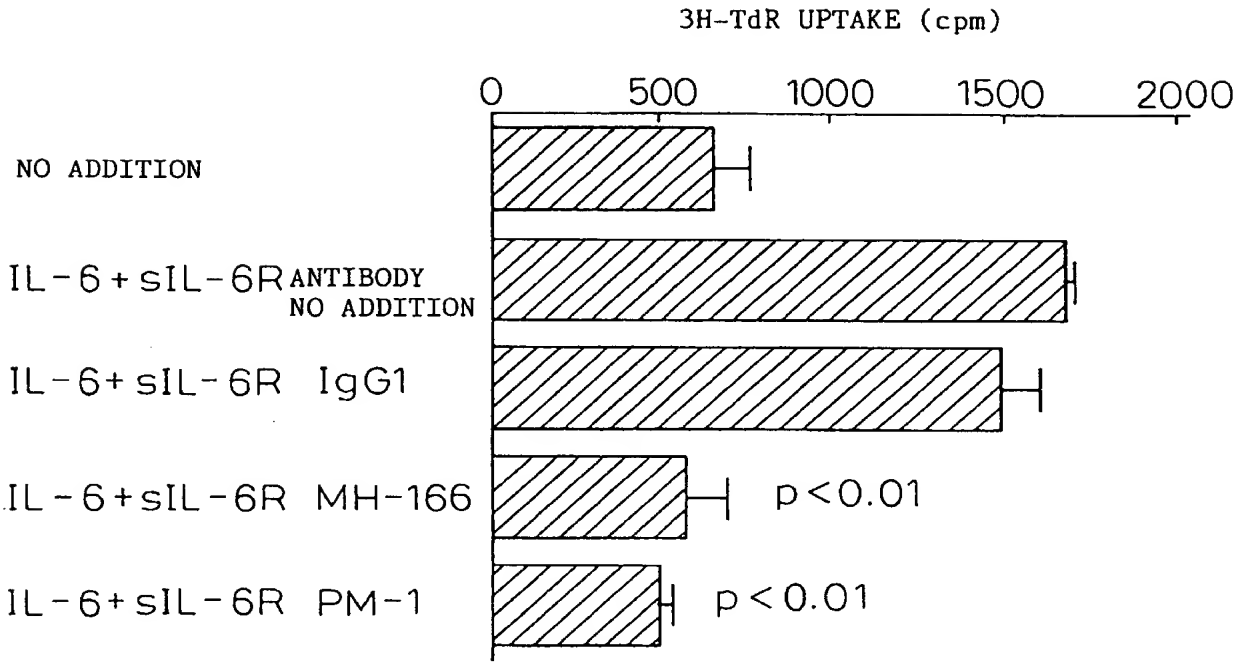

3H-TdR UPTAKE (cpm)
0
500
1000
1500
2000
NO ADDITION
IL-6 + sIL-6R ANTIBODY NO ADDITION
IL-6+sIL-6R IgG1
IL-6+sIL-6R MH-166
p<0.01
IL-6+sIL-6R PM-1
p<0.01

Fig. 4

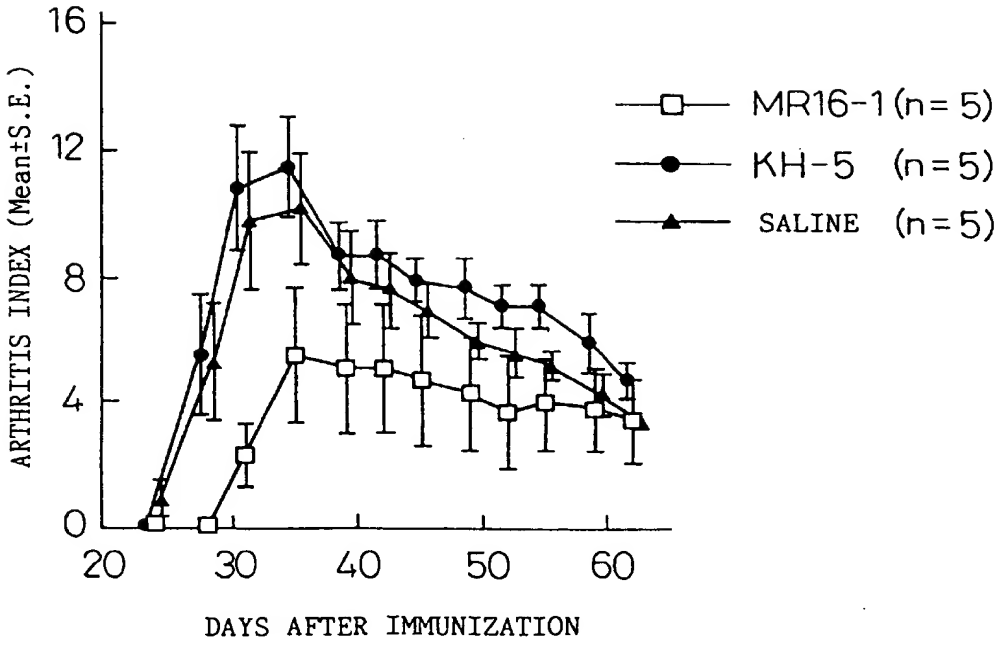

16
12
8
4
0
ARTHRITIS INDEX (Mean±S.E.)
20
30
40
50
60
DAYS AFTER IMMUNIZATION
MR16-1 (n=5)
KH-5 (n=5)
SALINE (n=5)

Fig. 5

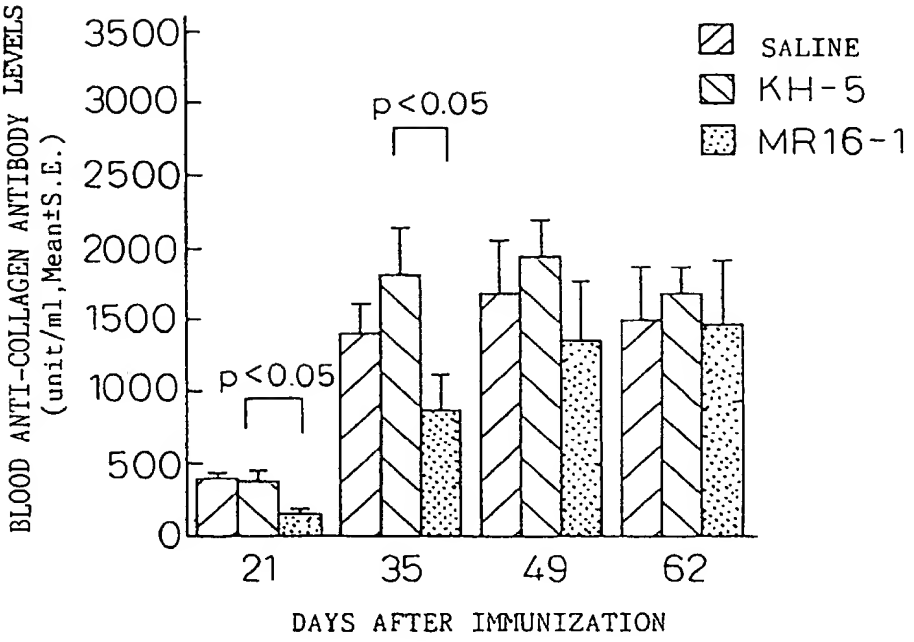

BLOOD ANTI-COLLAGEN ANTIBODY LEVELS
(unit/ml, Mean±S.E.)
3500
3000
2500
2000
1500
1000
500
0
p<0.05
p<0.05
SALINE
KH-5
MR16-1
21
35
49
62
DAYS AFTER IMMUNIZATION

FIG. 6(a)

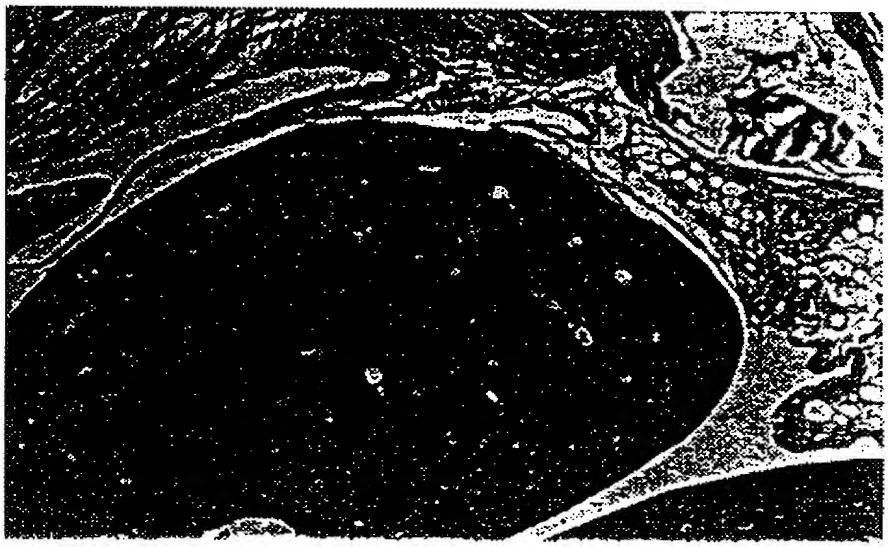
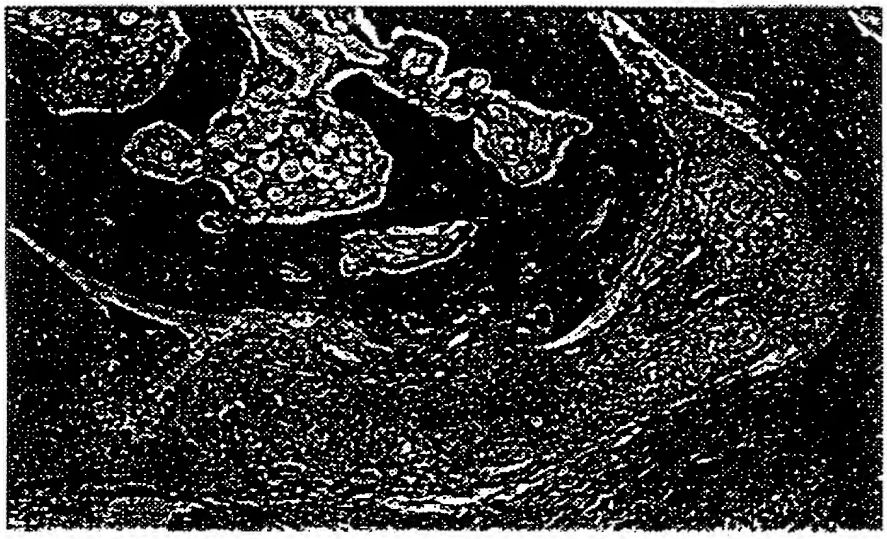


FIG. 6(b)



CHRONIC RHEUMATOID ARTHRITIS THERAPY CONTAINING IL-6 ANTAGONIST AS EFFECTIVE COMPONENT

RELATED APPLICATIONS

This application is a 35 USC § 371 application of PCT/JP95/01144, filed Jun. 7, 1995, and a continuation-in-part application of U.S. application Ser. No. 971,997 (Atty. Docket No. 53466/114), filed Feb. 21, 1997, which is a continuation of U.S. application Ser. No. 08/268,520, filed Jun. 30, 1994, abandoned.

TECHNICAL FIELD

The present invention relates to a chronic rheumatoid arthritis therapy or synovial cell growth inhibitor comprising an interleukin-6 antagonist as an effective component.

BACKGROUND ART

Chronic rheumatoid arthritis is a systemic chronic inflammatory disease in which abnormal growth of connective tissue, including synovial tissue, occurs in the joints (Melnyk et al., Arthritis Rheum. 33: 493–500, 1990). The joints of chronic rheumatoid arthritis patients have been shown to have marked growth of synovial cells, formation of a multilayer structure due to abnormal growth of the synovial cells (pannus formation), invasion of the synovial cells into cartilage tissue and bone tissue, vascularization toward the synovial tissue, and infiltration of inflammatory cells such as lymphocytes and macrophages. Mechanisms of onset of chronic rheumatoid arthritis have been reported to be based on such factors as heredity, bacterial infection and the contribution of various cytokines and growth factors, but the overall mechanism of onset has remained unclear.

In recent years, cytokines and growth factors including interleukin-1 (IL-1), interleukin-8 (IL-8), tumor necrosis factor α (TNFα), transforming growth factor β (TGFβ), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) have been detected in the synovial membrane and synovial fluid of chronic rheumatoid arthritis patients (Nouri et al., Clin. Exp. Immunol. 55:295–302, 1984; Thornton et al., Clin. Exp. Immunol. 86:79–86, 1991; Saxne, et al., Arthritis Rheum. 31:1041–1045, 1988; Seitz et al., J. Clin. Invest. 87:463–469, 1991; Lafyatis et al., J. Immunol. 143:1142–1148, 1989; Melnyk et al., Arthritis Rheum. 33:493–500, 1990).

It is believed that IL-1, TNFA and PDGF are particularly powerful synovial cell growth factors (Thornton et al., Clin. Exp. Immunol. 86:79–86, 1991; Lafyatis et al., J. Immunol. 143:1142–1148, 1989; Gitter et al., Immunology 66:196–200, 1989). It has also been suggested that stimulation by IL-1 and TNF results in production of interleukin-6 (IL-6) by synovial cells (Ito et al., Arthritis Rheum. 35:1197–1201, 1992).

IL-6 is a cytokine also known as B cell-stimulating factor 2 or interferon β2. IL-6 was discovered as a differentiation factor contributing to activation of B lymphoid cells (Hirano, T. et al., Nature 324, 73–76, 1986), and was later found to be a multifunction cytokine which influences the functioning of a variety of different cell types (Akira, S. et al., Adv. in Immunology 54, 1–78, 1993). Two functionally different membrane molecules are necessary for the induction of IL-6 activities. One of those is IL-6 receptor (IL-6R), an approximately 80 KD molecular weight, which binds specifically to IL-6.

IL-6R exists in a membrane-binding form which is expressed on the cell membrane and penetrates the cell membrane, as well as in the form of soluble IL-6R (sIL-6R) which consists mainly of the extracellular domain. Another protein is gp130 with a molecular weight of approximately 130 KD, which is non-ligand-binding but rather functions to mediate signal transduction. IL-6 and IL-6R form the complex IL-6/IL-6R which in turn binds with another membrane protein gp130, to induce the biological activity of IL-6 to the cell (Taga et al., J. Exp. Med. 196:967, 1987).

It has been reported that the serum or synovial fluid of chronic rheumatoid arthritis patients contains excessive amounts of interleukin-6 (IL-6) and soluble IL-6 receptor (sIL-6R) (Houssiau et al., Arthritis Rheum. 31:784–788, 1988; Hirano et al., Eur. J. Immunol. 18:1797–1801, 1988; Yoshioka et al., Japn. J. Rheumatol. in press), and since similar results have also been obtained in rheumatoid arthritis animal models (Takai et al., Arthritis Rheum. 32:594–600, 1989; Leisten et al. Clin. Immunol. Immunopathol. 56: 108–115, 1990), it has been suggested that IL-6 is somehow involved in chronic rheumatoid arthritis.

However, Japanese Unexamined Patent Publication No. 4-89433 discloses that peptides which strongly promote IL-6 production are effective as therapies for chronic rheumatoid arthritis.

Also, Higaki et al. have suggested that synovial cells from chronic rheumatoid arthritis patients have a low growth reaction against IL-6, and that IL-6 thus has an inhibitory function against growth of synovial cells (Clinical Immunology, 22:880–887, 1990). Thus, conflicting reports exist regarding the relationship between IL-6 and chronic rheumatoid arthritis, and the relationship is as yet unclear.

Recently, Wendling et al. have reported that administration of anti-IL-6 antibodies to chronic rheumatoid arthritis patients temporarily alleviates the clinical and biological symptoms, while also increasing IL-6 levels in the serum (J. Rheumatol. 20:259–262, 1993).

These reports provide no data at all about whether IL-6 accelerates growth of chronic rheumatoid arthritis synovial cells or has an inhibitory effect, and thus it is still unknown whether or not IL-6 has a direct effect on synovial cells of chronic rheumatoid arthritis patients.

DISCLOSURE OF THE INVENTION

Anti-inflammatory steroidal agents such as corticosteroids have been used as rheumatoid arthritis therapies, but since their continuous use induces undesirable side effects such as skin tissue damage and inhibition of adrenal cortex function, drugs with less side effects have been sought.

It is an object of the present invention to provide a novel chronic rheumatoid arthritis therapy without the disadvantages mentioned above. More specifically, the present invention provides a pharmaceutical composition for inhibiting abnormal growth of synovial cells in chronic rheumatoid arthritis, whose effective component is an interleukin-6 antagonist, as well as a pharmaceutical composition for treatment of a chronic rheumatoid arthritis having the same effect.

The present inventors have conducted diligent research on the role of IL-6 on synovial cells from rheumatoid arthritis, during which no growth of chronic rheumatoid arthritis synovial cells was found with IL-6 alone and a factor other than IL-6 was therefore investigated, and this has resulted in completion of the present invention based on the discovery that while IL-6 alone exhibits almost no growth effect on synovial cells, a powerful synovial cell growth effect occurs in the presence of both IL-6 and soluble IL-6R, and further that this synovial cell growth effect is suppressed by addition

of an antagonist which inhibits IL-6 activity, such as IL-6 antibody or IL-6R antibody.

In other words, the present invention relates to a pharmaceutical composition for treatment of a chronic rheumatoid arthritis comprising an IL-6 antagonist as the effective component. More specifically, the present invention relates to-a pharmaceutical composition for treatment of a chronic rheumatoid arthritis comprising an IL-6 antagonist as the effective component and suppressing abnormal growth of synovial cells. The present invention also relates to a synovial cell growth inhibitor whose effective component is an IL-6 antagonist.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing ^{3}H-thymidine uptake into synovial cells in the presence of either IL-6 or sIL-6R alone and in the presence of both IL-6 and sIL-6R.

FIG. 2 is a graph showing the effect of IL-6 antibody or IL-6R antibody on 3H-thymidine uptake into synovial cells in the presence of both IL-1β and sIL-6R.

FIG. 3 is a graph showing the effect of IL-6 antibody or IL-6R antibody on ^{3}H-thymidine uptake into synovial cells in the presence of both IL-6 and sIL-6R.

FIG. 4 is a graph showing the suppressive effect of IL-6R antibody on the onset of mouse collagen-induced arthritis models.

FIG. 5 is a graph showing serum anti-collagen antibody levels in arthritic mice.

FIG. 6 is a photograph of histopathological examination of hind paw joint of a collagen-arthritis mouse. (a) is a photograph from a mouse in an IL-6 receptor antibody-administered group, and (b) is from a mouse in a control antibody-administered group. In the IL-6 receptor antibody-administered group, invasion of granulation tissue into the cartilage and bone (chronic proliferative synovitis) was clearly suppressed.

DETAILED DESCRIPTION OF THE INVENTION

A pharmaceutical composition for treatment of a chronic rheumatoid arthritis according to the invention is a drug which when administered to chronic rheumatoid arthritis patients suppresses growth of synovial cells in joints and has an alleviating and therapeutic effect on the symptoms.

The IL-6 antagonist use-d according to the invention may be derived from any source so long as it is a substance which blocks IL-6 signal transfer and inhibits IL-6 biological activity. IL-6 antagonists include IL-6 antibody, IL-6R antibody, gp130 antibody, modified IL-6, antisense IL-6R and partial peptides of IL-6 or IL-6R.

An antibody used as an antagonist according to the invention, such as IL-6 antibody, IL-6R antibody or gp130 antibody, may be of any derivation or type (monoclonal, polyclonal), but monoclonal antibodies derived from mammalian animals are especially preferred. These antibodies bind to IL-6, IL-6R or gp130 to inhibit binding between IL-6 and IL-6R or IL-6R and gp130 and thus block IL-6 signal transduction, inhibiting IL-6 biological activity.

The animal species for the monoclonal antibody-producing cells is not particularly limited so long as it is a mammal, and human antibodies or antibodies derived from a mammal other than human may be used. Monoclonal antibodies derived from a mammal other than human are preferably monoclonal antibodies derived from rabbits or rodents because they are easier to prepare. There is no particular restriction on the rodents, but preferred examples are mice, rats and hamsters.

Examples of such antibodies which are IL-6 antibodies include MH166 (Matsuda et al., Eur. J. Immunol. 18:951–956, 1988) and SK2 antibody (Sato et al., Journal for the 21st General Meeting of the Japan Immunology Association, 21:116, 1991). Examples of IL-6R antibodies include PM-1 antibody (Hirata et al., J. Immunol. 143:2900–2906, 1989), AUK12-20 antibody, AUK64-7 antibody and AUK146-15 antibody (Intl. Unexamined Patent Application No. W092-19759). An example of gp130 antibody is AM64 antibody (Japanese Unexamined Patent Publication No. 3-219894).

Among these, PM-1 antibody is preferred.

Monoclonal antibodies may be prepared in the following manner which is based on a known technique. That is, IL-6, IL-6R or gp130 is used as the sensitizing antigen for immunization according to a conventional immunizing method, and the resulting immunocytes are then fused with known parent cells by a conventional cell fusion method and monoclonal antibody-producing cells are screened by a conventional screening method to prepare the antibodies.

More specifically, the monoclonal antibodies may be prepared in the following manner. For example, if the sensitizing antigen is human IL-6, the antibodies are obtained using the gene sequence for human IL-6 disclosed by Hirano et al., Nature, 324:73, 1986. The human IL-6 gene sequence is inserted into a publicly expression vector system and used to transform suitable host cells, after which the desired IL-6 protein is purified from the host cells or from the culture supernatant and the purified IL-6 protein is then used as the sensitizing antigen.

In the case of human IL-6R, the IL-6R protein may be obtained by the same method as for human IL-6 described above, using the gene sequence disclosed in European Patent Application No. EP325474. Two types of IL-6R exist, one expressed on the cell membrane and a soluble form (sIL-6R) which is separated from the cell membrane. sIL-6R consists mainly of the extracellular domain of IL-6R which is attached to the cell membrane, and it differs from the membrane-bound IL-6R in that it lacks the transmembrane domain or the transmembrane domain and the intracellular domain.

In the case of human gp130, the gp130 protein may be obtained by the same method as for human IL-6 described above, using the gene sequence disclosed in European Patent Application No. EP411946.

The mammalian animals immunized with the sensitizing antigen are not particularly restricted, but they are preferably selected -in consideration of their compatibility with the parent cells used for the cell fusion, and generally mice, rats, hamsters and rabbits may be used.

The immunization of the animals with the sensitizing antigen may be accomplished by a publicly known method. For example, a conventional method involves intraperitoneal or subcutaneous injection of the mammalian animals with the sensitizing antigen. Specifically, the sensitizing antigen is preferably diluted with an equivalent of PBS (Phosphate-Buffered Saline) or physiological saline, suspended and used together with a suitable amount of a conventional adjuvant such as Freund's complete adjuvant if desired, and then administered to the mammalian animals a few times every 4–21 days. An appropriate carrier may also be used for immunization with the sensitizing antigen.

After this immunization and confirmation of increased serum levels of the desired antibody, immunocytes are taken

from the mammalian animals and supplied for cell fusion, with especially preferred immunocytes being splenic cells.

The parent cells used for fusion with the above-mentioned immunocytes may be myeloma cells from mammalian animals, and a number of already publicly known cell strains may be suitably used, including P3 (P3x63Ag8.653) (J. Immunol. 123:1548, 1978), p3-U1 (Current Topics in Microbiology and Immunology 81:1–7, 1978), NS-1 (Eur. J. Immunol. 6:511–519, 1976), MPC-11 (Cell, 8:405–415, 1976), SP2/0 (Nature, 276:269–270, 1978), Of (J. Immunol. Meth. 35:1–21, 1980), S194 (J. Exp. Med. 148:313–323, 1978), R210 (Nature, 277:131–133, 1979). The cell fusion of the immunocytes with the myeloma cells may be based on a publicly known method, for example the method of Milstein et al. (Milstein et al., Methods Enzymol. 73:3–46, 1981).

More specifically, the above-mentioned cell fusion is carried out in a conventional nutrient culture in the presence of a cell fusion promoter. The fusion promoter used may be, for example, polyethylene glycol (PEG) or Sendai virus (HVJ), and if desired an aid such as dimethylsulfoxide may also be added to increase the fusion efficiency.

The proportions of the immunocytes and myeloma cells used are preferably a 1- to 10-fold amount of immunocytes with respect to the myeloma cells. The culturing medium used for the cell fusion may be, for example, RPMI1640 culture medium or MEM culture medium which are suitable for growth of myeloma cell strains, or other common culturing media used for such cell culturing, and supplementary serum solutions such as fetal calf serum (FCS) may also be used therewith.

The cell fusion is carried out by thoroughly mixing the prescribed amounts of the immunocytes and the myeloma cells in the culture medium described above, adding a PEG solution preheated to about 37° C., for example with PEG having an average molecular weight of about 1000 to 6000, to the culture medium usually at a concentration of 30 to 60% (w/v), and then mixing to form the desired fused cells (hybridomas). Next, the procedure of gradual addition of a suitable culture medium and centrifugation to remove the supernatant is repeated, to accomplish removal of the cell fusing agent, etc. which is unfavorable for growth of the hybridomas.

Suitable hybridomas are selected by culturing in a normal selective culture medium, such as HAT culture medium (containing hypoxanthine, aminopterin and thymine). The culturing in the HAT culture medium is continued for a given time, usually a few days to a few weeks, sufficient for death of the cells other than the hybridomas (non-fused cells). Next, normal limited dilution is carried out, and the hybridomas producing the desired antibodies are subjected to masking and monocloning.

The monoclonal antibody-producing hybridomas prepared in this manner may be subcultured in a common culture solution and they may also be placed in liquid nitrogen for long-term storage.

In order to acquire the monoclonal antibodies from the hybridomas, the hybridomas are cultured according to a conventional method after which the culture supernatant is recovered, or else a method is used whereby the hybridomas are injected to a compatible mammalian animal, grown, and the ascites fluid is obtained. The former method is suited for obtaining high purity antibodies, while the latter method is suited for mass production of the antibodies.

The monoclonal antibodies obtained by these methods may then be purified to a high degree using conventional purification means, such as salting-out, gel filtration, affinity chromatography or the like.

The monoclonal antibodies prepared in this manner may then be checked for high sensitivity and high purity recognition of the antigen by common immunological means such as radioimmunoassay (RIA), enzyme-linked immunoassay, (EIA, ELISA), the fluorescent antibody technique (immunofluorescence analysis), etc.

The monoclonal antibodies used according to the invention are not limited to monoclonal antibodies produced by hybridomas, and they may be ones which have been artificially modified for the purpose of lowering the heteroantigenicity against humans. For example, a chimeric antibody may be used which consists of the variable region of a monoclonal antibody of a mammalian animal other than human, such as a mouse, and the constant region of a human antibody, and such a chimeric antibody may be produced by a known chimeric antibody-producing method, particularly a gene recombination technique.

Reshaped human antibodies may also be used according to the invention. These are prepared by using the complementary determinant region of a mouse or other non-human mammalian animal antibody to replace the complementary determinant region of a human antibody, and conventional gene recombination methods therefor are well-known. One of the known methods may be used to obtain a reshaped human antibody which is useful according to the invention. A preferred example of such a reshaped human antibody is hPM-1 (see Intl. Unexamined Patent Application No. W092-19759).

When necessary, amino acids of the framework (FR) region of the variable region of an antibody may be substituted so that the complementary determinant region of the reshaped human antibody forms a suitable antibody binding site (Sato et al., Cancer Res. 53:851–856, 1993). In addition, the object stated above may also be achieved by constructing a gene coding for an antibody fragment which binds to the antigen to inhibit IL-6 activity, such as Fab or Fv, or a single chain Fv (scFv) wherein the Fv of the H and L chains are attached via an appropriate linker, and using it for expression in appropriate host cells (see, for example, Bird et al., TIBTECH, 9:132–137, 1991; Huston et al., Proc. Natl. Acad. Sci. USA, 85:5879–5883, 1988).

Modified IL-6 used according to the invention may be the one disclosed by Brakenhoff et al, J. Biol. Chem. 269:86–93, 1994 or Savino et al., EMBO J. 13:1357–1367, 1994.

The modified IL-6 used may be obtained by introducing a mutation such as a substitution, deletion or insertion into the IL-6 amino acid sequence to maintain the binding activity with IL-6R while eliminating the IL-6 signal transfer function. The IL-6 source may be from any animal species so long as it has the aforementioned properties, but in terms of antigenicity, a human derived one is preferably used.

Specifically, the secondary structure of the IL-6 amino acid sequence may be predicted using a publicly known molecular modeling program such as WHATIF (Vriend et al., J. Mol. Graphics, 8:52–56, 1990), whereby the influence of mutated amino acid residues on the entire structure may also be evaluated. After determining appropriate mutated amino acid residues, a vector containing the nucleotide sequence coding for the human IL-6 gene is used as a template for introduction of the mutation by the conventionally employed PCR (polymerase chain reaction) method, to obtain a gene coding for the modified IL-6. This is then incorporated into a suitable expression vector if necessary

and expressed in *E. coli* cells or mammalian cells, and then used either while in the culture supernatant or after isolation and purification by conventional methods, to evaluate the binding activity for IL-6R and the neutralized IL-6 signal transfer activity.

An IL-6 partial peptide or IL-6R partial peptide used according to the present invention may have any sequence so long as it binds to IL-6R or IL-6, respectively, and has no IL-6 activity transfer function. IL-6 partial peptides and IL-6R partial peptides are described in U.S. Pat. No. 5,210,075. An IL-6 antisense oligonucleotide is described in Japanese Patent Application No. 5-300338.

A pharmaceutical composition for treatment of chronic rheumatoid arthritis whose effective component is an IL-6 antagonist according to the invention is effective for treatment of chronic rheumatoid arthritis if it blocks IL-6 signal transduction and suppresses abnormal growth of synovial cells induced by IL-6, which are implicated in the disease. Example 1 demonstrates the in vitro growth suppressing effect on rheumatic patient-derived synovial cells. In Example 2, IL-6 receptor antibody was administered to mice arthritic models immunized with type II collagen, and the relevant data demonstrates (1) suppression of onset of arthritis on the basis of an arthritis index (FIG. 4), (2) suppression of anti-type II collagen antibody production in the blood of collagen-immunized mice (FIG. 5) and (3) suppression of granulation tissue invasion into cartilage and bone (chronic proliferative synovitis) in the hind paw joints of mice arthritic models administered IL-6 receptor antibody (FIG. 6).

In regard to (1) and (2) above, the results confirmed a suppressing effect by IL-6 receptor antibody, especially initially, on onset of arthritis in the mice models. The results of (3) demonstrated that invasion of granulation tissue into the cartilage and bone tissue is suppressed, and this supports the results obtained in Example 1 (in vitro inhibition of synovial cell growth).

The experimental results of (1) and (2) indicate that the pharmaceutical composition for treatment of chronic rheumatoid arthritis of the present invention has an excellent initial effect on rheumatoid arthritis.

The pharmaceutical composition for treatment of chronic rheumatoid arthritis of the invention is preferably administered parenterally, for example by intravenous, intramuscular, intraperitoneal or subcutaneous injection, either systemically or locally. Also, it may be in the form of a medical formulation kit together with at least one type of medical carrier or diluent.

The dosage of the pharmaceutical composition for treatment of chronic rheumatoid arthritis of the invention when administered to humans will differ depending on pathological condition and age of the patient, and the mode of administration, and thus suitable and appropriate doses must be selected. As an example, a maximum of 4 divided doses in the range of about 1 to 1000 mg/patient may be selected. However, the pharmaceutical composition for treatment of rheumatoid arthritis of the invention is not limited to these dosages.

The pharmaceutical composition for treatment of rheumatoid arthritis of the invention may be formulated according to conventional methods. For example, an injection formulation is prepared by dissolving the purified IL-6 antagonist in a solvent such as physiological saline or a buffer solution and then adding an adsorption inhibitor such as Tween 80, gelatin, human serum albumin (HSA) or the like, and the mixture may be lyophilized prior to use for solution reconstitution. The excipient used for lyophilization may be a sugar alcohol such as mannitol or glucose, or a saccharide.

EXAMPLES

The present invention will now be explained in more detail by way of the following examples, reference examples and experimental examples, with the understanding that the invention is in no way restricted thereto.

Reference Example 1

Preparation of human soluble IL-6 receptor

Soluble IL-6R was prepared (Yasukawa et al., J. Biochem. 108:673–676, 1990) by the PCR (polymerase chain reaction) method using plasmid pBSF2R.236 containing cDNA coding for human IL-6 receptor (IL-6R) obtained according to the method of Yamasaki et al. (Science, 241:825–828, 1988).

The aforementioned plasmid pBSF2R.236 was digested with restriction enzyme SphI to obtain an IL-6R cDNA fragment which was then inserted into mp18 (Amersham Co.). The synthetic oligoprimer ATATTCTCTAGAGAGATTCT designed for introduction of a stop codon in IL-6R cDNA was used to introduce a mutation in the IL-6R cDNA by the PCR method using an Invitro Mutagenesis System (Amersham Co.). This procedure resulted in introduction of a stop codon at the position of amino acid 345 to obtain cDNA coding for soluble IL-6R (sIL-6R).

In order to express the sIL-6R cDNA in CHO cells, the aforementioned sIL-6R cDNA cut with HindIII-SalI was inserted into plasmid pECEdhfr (Clauser et al., Cell, 45:721–735, 1986) which had cDNA coding for dihydrofolate reductase (dhfr) inserted at the restriction enzyme PvuI cleavage site, to obtain the CHO cell expression plasmid pECEdhfr344.

A 10 μg of plasmid pECEdhfr344 was used for transfection of the dhfr$^-$CHO cell line DXB-11 (Urland et al., Proc. Natl. Acad. Sci. USA 77, 4216–4220, 1980) by the calcium phosphate precipitation method (Chen et al., Mol. Cell. Biol. 7:2745–2751, 1987).

The transfected CHO cells were cultured for 3 weeks in a nucleoside-free αMEM selective culture medium containing 1 mM glutamine, 10% dialyzed Fetal Calf Serum (FCS), 100 U/ml penicillin and 100 μg/ml streptomycin. The selected CHO cells were screened by the limiting dilution method, and a single monoclonal CHO cell line was obtained. The CHO cell clone was amplified in 20 nM to 200 nM concentration methotrexate (MTX), to obtain the human SIL-6R-producing CHO cell line 5E27.

The CHO cell line 5E27 was cultured in Iscove's modified Dulbecco's medium (IMDM, product of Gibco Co.) containing 5% FCS, the culture supernatant was recovered, and the sIL-6R concentration in the culture supernatant was measured by the ELISA (Enzyme-Linked Immunosorbent Assay) method according to the common procedure.

Reference Example 2

Preparation of human IL-6 antibody

Human IL-6 antibody was prepared according to the method of Matsuda et al. (Eur. J. Immunol. 18:951–956, 1988).

BALB/c mice were immunized with 10 μg of recombinant IL-6 (Hirano et al., Immunol. Lett., 17:41, 1988) together

with Freund's complete adjuvant, and this was continued once a week until anti-IL-6 antibodies were detected in the blood serum.

Immunocytes were extracted from the local lymph nodes, and polyethylene glycol 1500 was used for fusion with the myeloma cell line P3U1. Hybridomas were selected according to the method of Oi et al. (Selective Methods in Cellular Immunology, W. H. Freeman and Co., San Francisco, 351, 1980) using HAT culture medium, and a human IL-6 antibody-producing hybridoma line was established. The human IL-6 antibody-producing hybridoma was subjected to IL-6 binding assay in the following manner.

Specifically, a soft polyvinyl 96-well microplate (product of Dynatech Laboratories, Inc., Alexandria, Va.) was coated overnight with 100 μl of goat anti-mouse Ig antibody (10 μl/ml, product of Cooper Biomedical, Inc., Malvern, Pa.) in a 0.1M carbonate-hydrogen carbonate buffer solution (pH 9.6) at 4° C. The plate was then treated for 2 hours at room temperature with PBS containing 100 μl of 1% bovine serum albumin (BSA). After washing with PBS, 100 μl of hybridoma culture supernatant was added to each well, and incubation was conducted overnight at 4° C.

The plates were then washed and ^{125}I-labelled recombinant IL-6 was added to each well to 2000 cpm/0.5 ng/well, and after washing, the radioactivity of each well was measured with a gamma counter (Beckman Gamma 9000, Beckman Instruments, Fullerton, Calif.). Of 216 hybridoma clones, 32 hybridoma clones were positive for the IL-6 binding assay. Among these clones there was finally obtained the stable clone MH166.BSF2. The IL-6 antibody MH166 produced by this hybridoma has an IgG1K subtype.

The IL-6-dependent mouse hybridoma cell line MH60.BSF2 (Matsuda et al., Eur. J. Immunol. 18:951–956, 1988) was then used to determine the neutralizing activity of MH166 antibody on growth of the hybridoma. MH60.BSF2 cells were dispensed at an amount of 1×10^4/200 μl/well, a sample containing MH166 antibody was added thereto, culture was performed for 48 hours, and 15.1 Ci/mmol of ^{3}H-thymidine (New England Nuclear, Boston Mass.) was added, after which culture was continued for 6 hours.

The cells were placed on glass filter paper and treated with an automatic harvester (Labo Mash Science Co., Tokyo, Japan). Rabbit anti-IL-6 antibody was used as a control. As a result, MH166 antibody inhibited uptake of ^{3}H-thymidine by the MH60.BSF2 cells in a dose-dependent manner. This demonstrated that MH166 antibody neutralizes IL-6 activity.

Reference Example 3

Preparation of human IL-6 receptor antibody

Anti-IL-6R antibody MT18 constructed by the method of Hirata et al. (J. Immunol., 143:2900–2906, 1989) was bound to Sepharose 4B (product of Pharmacia Fine Chemicals, Piscataway, N.J.) activated with CNBr, according to the accompanying instructions, and the bound complex was used to purify IL-6R (Yamasaki et al., Science 241:825–828, 1988).

The human myeloma cell line U266 was solubilized with 1 mM p-paraaminophenylmethane sulfonylfluoride hydrochloride (product of Wako Chemicals) containing 1% digitonin (product of Wako Chemicals), 10 mM triethanolamine (pH 7.8) and 0.15M NaCl (digitonin buffer solution), and mixed with MT18 antibody bound to Sepharose 4B beads. The beads were then washed 6 times with digitonin buffer solution to obtain partially purified IL-6R for immunization.

BALB/c mice were immunized 4 times every 10 days with the partially purified IL-6R obtained from 3x10 U266 cells, and then hybridomas were prepared by conventional methods. The culture supernatants of the hybridomas from the growth-positive wells were examined for IL-6 binding activity by-the following method. After labelling 5×10^7 U266 cells with ^{35}S-methionine (2.5 mCi) they were solubilized with the aforementioned digitonin buffer solution. The solubilized U266 cells were mixed with a 0.04 ml of MT18 antibody bound to Sepharose 4B beads, and after washing 6 times with digitonin buffer solution, the ^{35}S-methionine-labelled IL-6R was washed off with 0.25 ml of digitonin buffer solution (pH 3.4) and neutralized with 0.025 ml of 1M Tris (pH 7.4).

A 0.05 ml of the hybridoma culture supernatant was mixed with 0.01 ml of Protein G Sepharose (product of Pharmacia). After washing, the Sepharose was incubated with 0.005 ml of the ^{35}S-labelled IL-6R solution prepared earlier. The immunoprecipitated substance was analyzed by SDS-PAGE, and the hybridoma culture supernatants reacting with IL-6R were examined. As a result, a reaction-positive hybridoma clone PM-1 was established. The IL-6R antibody PM-1 produced by hybridoma PM-1 has an IgG1K subtype.

The inhibiting activity of the antibody produced by hybridoma PM-1 against binding of IL-6 to human IL-6R was investigated using the human myeloma cell line U266. Human recombinant IL-6 was prepared with *E. coli* (Hirano et al., Immunol. Lett., 17:41, 1988) and ^{125}I-labelled with Bolton-Hunter reagent (New England Nuclear, Boston, Mass.) (Taga et al., J. Exp. Med. 166:967, 1987).

4×10^5 U266 cells were cultured at room temperature in the presence of a 100-fold excess of non-labelled IL-6 for one hour, together with 70% (v/v) of hybridoma PM-1 culture supernatant and 14000 cpm of ^{125}I-labelled IL-6. A 70 μl sample was overlaid onto 300 μl of FCS placed in a 400 μl microfuge polyethylene tube, and after centrifugation the radioactivity on the cells was measured.

As a result it was demonstrated that the antibodies produced by hybridoma PM-1 inhibited binding of IL-6 to IL-6R.

Reference Example 4

Preparation of mouse IL-6 receptor antibody

Monoclonal antibodies against mouse IL-6 receptor were prepared by the method described in Japanese Patent Application No. 6-134617.

Following the method of Saito et al. (J. Immunol., 147, 168–173, 1993), CHO cells producing mouse soluble IL-6 receptor were cultured in IMDM medium containing 10% FCS, and the mouse soluble IL-6 receptor was purified from the culture supernatant using the mouse soluble IL-6 receptor antibody RS12 (see ibid. Saito et al.) and an affinity column immobilizing Affigel 10 gel (Biorad).

A 50 μg of the obtained mouse soluble IL-6 receptor was mixed with Freund's complete adjuvant and intraperitoneally injected into Wistar rats (Nihon Charles River Co.). Booster immunizations were given with Freund's incomplete adjuvant after 2 weeks. On the 45th day the rats were butchered, and about 2×10^8 splenic cells thereof were used for cell fusion with 1×10^7 mouse P3U1 myeloma cells by a conventional method utilizing 50% PEG1500 (Berlinger Mannheim), after which the hybridomas were screened with HAT medium.

After adding the hybridoma culture supernatants to an immunoplate coated with rabbit anti-rat IgG antibody (Cappel Co.), mouse soluble IL-6 receptor was reacted

therewith and the hybridomas producing antibodies against mouse soluble IL-6 receptor were screened by the ELISA method using rabbit anti-mouse IL-6 receptor antibody and alkali phosphatase-labelled sheep anti-rabbit IgG. The hybridoma clones in which antibody production was confirmed were subjected to subscreening twice to obtain a single hybridoma clone. This clone was named MR16-1.

The neutralizing activity of the antibody produced by this hybridoma against mouse IL-6 signal transduction was investigated by incorporation of ^{3}H-thymidine using MH60.BSF2 cells (Matsuda et al., J. Immunol. 18, 951–956, 1988), MH60.BSF2 cells were added to a 96-well plate to 1×10^4 cells/200 μl/well, and then mouse IL-6 (10 μg/ml) and MR16-I antibody or RS12 antibody were added to 12.3–1000 ng/ml prior to culturing at 37° C., in 5% CO_2 for 44 hours, after which 3H-thymidine (1 μCi/well) was added and the uptake after 4 hours was measured. As a result, MR16–1 antibody was found to inhibit uptake of ^{3}H-thymidine by MH60.BSF2 cells.

Experiment 1

Establishment of chronic rheumatoid arthritis-derived synovial cell line

(1) Preparation of synovial cells

Synovial tissue was obtained during surgical operation on the joint of a chronic rheumatoid arthritis patient. The synovial tissue was minced with scissors and then subjected to enzymatic dissociation by incubation for one hour at 37° C. with 5 mg/ml of TYPE I collagenase (product of Sigma Chemical Co.) and 0.15 mg/ml of bovine pancreatic DNase (product of Sigma Chemical Co.) in IMDM (Iscove's modified Dulbecco's medium), and passed through a mesh to obtain singule cells. These obtained cells were then cultured overnight in a culture flask using IMDM containing 5% FCS, after which the non-adherent cells were removed to obtain the synovial cells. The synovial cells were passaged 3 to 6 times and used for the following experiment.

(2) IL-6 production by synovial cells

The synovial cells obtained as described above were suspended in IMDM culture medium containing 5% FCS (product of Hyclone Laboratories Inc.), 10 U/ml of penicillin G and 100 μg/ml streptomycin to an amount of 3×10^3 cells/well, and were then cultured in 96-well microtiter plate (product of Falcon Co.), which human interleukin-1β (IL-1β), human tumor necrosis factor α (TNFα), human platelet-derived growth factor (PDGF)AB and human basic fibroblast growth factor (bFGF) were added to concentrations of 0.01 or 0.1, 0.1 or 1, 1 or 10 and 1 or 10 ng/ml, respectively, and upon culturing at 37° C. for 72 hours the culture supernatants were collected.

A 100 μl of anti-human IL-6 antibody MH166 (1 μg/ml) was added to a 96-well ELISA plate (Immunoplate: product of Nunc Co.) and incubated at 4° C. for 24 hours. Each well was subsequently washed with PBS containing 0.05% Tween20, and blocked at 4° C. overnight with PBS containing 1% BSA. The culture supernatants obtained previously were then diluted with PBS containing 1% BSA, added to the wells, and then incubated at room temperature for 2 hours. After washing with PBS containing 0.05% Tween20, 2.5 μg/ml of rabbit polyclonal anti-human IL-6 antibody purified with a 100 μl protein A column (product of Pharmacia) was added.

After incubating at room temperature for 2 hours, the rabbit polyclonal anti-IL-6 antibody binding to IL-6 in the culture supernatants was reacted with alkali phosphatase-bound anti-rabbit IgG antibody (product of Tago Co.). And then 1 mg/ml of Sigma104 alkali phosphatase substrate (product of Sigma Co.) was added according to the attached instructions and the absorbance at 405–600 nm was measured with an MPR A4 microplate reader (product of Tosoh Co.).

Calibration curves were prepared for the recombinant IL-6 during each assay for conversion of the absorbance OD values to human IL-6 concentrations. The results are given in Table 1.

TABLE 1

Augmented IL-6 production from synovial cell

Treatment (ng/ml)		IL-6 (ng/ml)
Untreated		0.096 ± 0.012
IL-1β	0.01	6.743 ± 0.178
	0.1	17.707 ± 0.259
TNFα	0.1	0.575 ± 0.008
	1	1.688 ± 0.034
PDGF-AB	1	0.163 ± 0.035
	10	0.165 ± 0.016
bFGF	1	0.181 ± 0.009
	10	0.230 ± 0.019

Note: The synovial cells were cultured for 3 days with IL-1β, TNFα, PDGF-AB or bFGF. After culture, the IL-6 concentrations of the supernatants were measured by ELISA.

The results demonstrated that IL-1β strongly promotes IL-6 production by synovial cells.

Example 1

(1) The synovial cells obtained in Experiment 1 (3×10^3/well) were suspended in IMDM culture medium containing 5% FCS (product of Hyclone Laboratories, Inc.), 10 U/ml of penicillin G and 100 μg/ml of streptomycin and were then added into a 96-well microtiter plate (#3072, product of Falcon Co.) and cultured for 5 days in the presence of various concentrations of IL-6 or sIL-6 alone, or in the presence of both IL-6 and sIL-6R. At 72 hours after starting the culturing, ^{3}H-thymidine (product of Amersham International plc) was added to each well to 1 μCi/well, and after the culturing was completed the radioactivity in the cells was measured with a scintillation counter. The results are shown in FIG. 1.

As a result, the ^{3}H-thymidine uptake of the synovial cells was low with IL-6 or sIL-6R alone, and no growth of synovial cells was observed. In contrast, in the presence of at least a 10 ng/ml concentration of IL-6 and 100 ng/ml concentration of sIL-6R, significant uptake of ^{3}H-thymidine was observed compared to the control group. Thus, while virtually no growth effect on synovial cells was exhibited with IL-6 alone, in the presence of both IL-6 and sIL-6R a powerful synovial cell growth effect was clearly produced.

(2) Synovial cells (3×10^3/well) were cultured in the presence of a sufficient amount of IL-β to produce IL-6 (0.1 ng/ml), 100 ng/ml of sIL-6R and 25 μg/ml of IL-6 antibody or 25 μg/ml of IL-6R antibody. At 72 hours after the start of culturing, ^{3}H-thymidine was added to each well to 1 μCi/well, and after the culture was completed the radioactivity in the cells was measured with a scintillation counter. The results are shown in FIG. 2. Addition of IL-6 antibody or IL-6R antibody completely suppressed the growth of synovial cells augmented by sIL-6R.

(3) Synovial cells (3×10^3/well) were cultured in the presence of 100 ng/ml of IL-6 (product of Genzyme Co.), 100 ng/ml of sIL-6R and 25 μg/ml of IL-6 antibody or IL-6R

antibody, which were obtained in the above-mentioned Reference Examples. At 72 hours after the start of culture, ^{3}H-thymidine was added to each well to 1 μCi/well, and after the culture was completed, the radioactivity in the cells was measured with a scintillation counter. The results are shown in FIG. 3. Addition of IL-6 antibody or IL-6R antibody completely suppressed the growth of synovial cells augmented by sIL-6R.

Example 2

The suppressing effect of IL-6 receptor antibody on onset of arthritis was investigated using a mouse arthritis model.

A bovine type II collagen solution (Collagen Technology Research Group) (4 mg/ml) dissolved in a 0.1N aqueous acetic acid solution and complete adjuvant H37Ra (DIFCO) were mixed in equivalent amounts, to prepare an adjuvant. A 100 μl of the adjuvant was subcutaneously injected at the base of tail of 8- to 9-week-old female DBA/1J mice (Charles River Japan). An additional 100 μl was injected 20 days later under the dorsal skin to induce arthritis.

Mouse IL-6 receptor antibody MR16-1 was intravenously administered at 2 mg per mouse upon first collagen sensitization, and each mouse was subcutaneously injected with an additional 0.5 mg (n=5) each week thereafter for 7 weeks. As a control, anti-DNP antibody KH-5 (Chugai Seiyaku) of the same isotype was used (n=5).

The severity of arthritis was evaluated based on an arthritis index. The evaluation was based on a 4 point scale for each limb, for a total of 16 points per individual. The evaluation standard was as follows.

0.5: Erythema observed at one site of joint.

1: Erythema observed at two sites of joint, or redness but no swelling of dorsa.

2: Moderate swelling observed.

3: Severe swelling of pedal dorsa, but not reaching all of the digits.

4: Severe swelling of pedal dorsa and digits.

The results are shown in FIG. 4. Onset of arthritis from early stage arthritis was clearly suppressed in the IL-6 receptor antibody-administered group, compared to the control antibody-administered group.

On the other hand, the results of measurement of the anti-type II collage antibody titer in the mouse blood showed a significant reduction from early stage arthritis in the IL-6 receptor antibody-administered group compared to the control antibody-administered group (FIG. 5).

The mice were sacrificed on the 35th day after collagen immunization, and the hind legs were fixed with 20% formalin. They were then subjected to demineralization in an EDTA solution (pH 7.6) and dewatering with alcohol. They were subsequently wrapped in paraffin and cut to 2 μm thick sections. The sections were stained with hematoxylin and eosin and observed under 125×magnification (FIG. 6). As a result, invasion of granulation tissue into the cartilage and bone, i.e. chronic proliferative synovitis was suppressed in the IL-6 receptor antibody-administered group compared to the control antibody-administered group.

IL-6 is a cytokine which induces differentiation of B cells into antibody-produc-ing cells. IL-6 also promotes proliferation of synovial cells in the presence of IL-6 receptor. Since in mouse collagen arthritis models, anti-IL-6 receptor antibody significantly suppressed anti-type II collagen antibody titers on the 21st and 35th days after collagen sensitization, compared to the control antibody-administered group, it is believed that the antibody production inhibition by anti-IL-6 receptor antibody is one factor responsible for the suppressing effect on arthritis. Moreover, although no suppression of antibody production was observed from the 49th day after collagen sensitization, the fact that an adequate suppressing effect on onset of arthritis was exhibited even during this period, and that HE staining of tissue surrounding the tarsal bone showed suppressed invasion of granulation tissue into the cartilage and bone of the anti-IL-6 receptor antibody-administered group compared to the control group, the synovial growth-suppressing effect is also believed to contribute to the arthritis-inhibiting effect.

INDUSTRIAL APPLICABILITY

Synovial cells from chronic rheumatoid arthritis patients proliferate in the presence of both IL-6 and sIL-6R. The fact that synovial fluid of chronic rheumatoid arthritis patients contains a sufficient amount of IL-6 and sIL-6R to induce growth of synovial cells suggests that signal transduction by IL-6 is involved in abnormal growth of synovial cells in chronic rheumatoid arthritis.

It has thus been conclusively demonstrated that a chronic rheumatoid arthritis therapy whose effective component is an IL-6 antagonist according to the present invention suppresses growth of synovial cells in chronic rheumatoid arthritis patients in the presence of IL-6 and sIL-6R, and thus has a therapeutic effect against chronic rheumatoid arthritis. Consequently, the IL-6 antagonist of the invention is useful as a therapeutic agent for chronic rheumatoid arthritis-in which abnormal growth of synovial cells occurs.

What is claimed is:

1. A method for inhibiting synovial cell growth, comprising administering to a patient in need thereof a pharmaceutical composition comprising an interleukin-6 antagonist and a physiologically acceptable carrier.

2. The method according to claim **1**, wherein the interleukin-6 antagonist is selected from the group consisting of an interleukin-6 antibody and an interleukin-6 receptor antibody.

3. The method according to claim **2**, wherein the antagonist is a monoclonal antibody.

4. The method according to claim **1**, wherein the patient is a human.

5. The method according to claim **4**, wherein the antagonist is administered in four divided doses of from about to 1000 mg.

6. A method of treating chronic rheumatoid arthritis, comprising administering to a patient in need thereof a pharmaceutical composition comprising an antibody against an interleukin-6 receptor and a physiologically acceptable carrier.

7. The method according to claim **6**, wherein the antibody suppresses abnormal growth of synovial cells.

8. The method according to claim **6**, wherein the antibody is an antibody against a human interleukin-6 receptor.

9. The method according to claim **6**, wherein the antibody is a monoclonal antibody.

10. The method according to claim **6**, wherein the patient is a human.

11. The method according to claim **10**, wherein the antibody is administered in four divided doses of from about 1 to 1000 mg.

* * * * *

EXHIBIT 3
4th and 8th YEAR MAINTENANCE FEE STATEMENTS

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MAINTENANCE FEE STATEMENT

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Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,888,510	**$880.00**	**$0.00**	**09/06/02**	**08/817,084**	**03/30/99**	**04/07/97**	**04**	**NO**	**53466/200**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,888,510	**$2,300.00**	**$0.00**	**09/08/06**	**08/817,084**	**03/30/99**	**04/07/97**	**08**	**NO**	**53466/200**

EXHIBIT 4
ACTEMRA® FULL PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACTEMRA safely and effectively. See full prescribing information for ACTEMRA.

ACTEMRA® (tocilizumab)
Injection, for intravenous infusion
Initial U.S. Approval: year

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.
- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)**
- **If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

INDICATIONS AND USAGE

ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor inhibitor indicated for treatment of:

Rheumatoid Arthritis (1)
- Adult patients with moderately-to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis (2.1)

ACTEMRA may be used alone or in combination with methotrexate or other DMARDs.

Recommended Adult Dosage Every 4 Weeks	
Patients who have had an inadequate response to one or more TNF antagonists	When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response.

- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000/mm^3, platelet count below 100,000/mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN). (2.1, 5.3)
- ACTEMRA doses exceeding 800 mg per infusion are not recommended. (2.1, 12.3)

Administration (2.2)
- Dilute to 100 mL in 0.9% Sodium Chloride for intravenous infusion using aseptic technique.
- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

Dose Modifications (2.3)
- Recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

DOSAGE FORMS AND STRENGTHS

Single-use vials of ACTEMRA (20 mg/mL):
- 80 mg/ 4 mL (3)
- 200 mg/ 10 mL (3)
- 400 mg/ 20 mL (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Serious Infections – do not administer ACTEMRA during an active infection, including localized infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk. (5.2)
- Laboratory monitoring – recommended due to potential consequences of treatment related changes in neutrophils, platelets, lipids, and liver function tests. (2.3, 5.3)
- Anaphylaxis or serious hypersensitivity reactions have occurred. (5.5)
- Live vaccines – should not be given with ACTEMRA. (5.8, 7.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data, may cause fetal harm. Pregnancy registry available. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Issued: MM/YYYY

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

ACTEMRA® (tocilizumab) is indicated for the treatment of adult patients with moderately-to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis

ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other DMARDs. The recommended dose of ACTEMRA for adult patients given once every 4 weeks as a 60-minute single intravenous drip infusion is:

Recommended Adult Dosage Every 4 Weeks	
Patients who have had an inadequate response to one or more TNF antagonists	• When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response

- ACTEMRA has not been studied and its use should be avoided in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection.
- It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000/mm^3, platelet count below 100,000/mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).

- Reduction of dose from 8 mg/kg to 4 mg/kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.3), Warnings and Precautions (5.3), and Adverse Reactions (6.1)]*.
- Doses exceeding 800 mg per infusion are not recommended *[see Clinical Pharmacology (12.3)]*.

2.2 General Considerations for Administration

ACTEMRA for intravenous infusion should be diluted to 100 mL by a healthcare professional using aseptic technique as follows:

1. From a 100 mL infusion bag or bottle, withdraw a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA solution required for the patient's dose.
2. Slowly add ACTEMRA for intravenous infusion from each vial into the infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.
3. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used. Fully diluted ACTEMRA solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.
4. The fully diluted ACTEMRA solutions for infusion may be stored at 2-8°C (36-46°F) or room temperature for up to 24 hours and should be protected from light. ACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
5. Allow the fully diluted ACTEMRA solution to reach room temperature prior to infusion.
6. The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.
7. ACTEMRA should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ACTEMRA with other drugs.

2.3 Dosage Modifications

ACTEMRA treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3)]*:	
Lab Value	**Recommendation**
> 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range, reduce ACTEMRA dose to 4 mg/kg or interrupt ACTEMRA until ALT/AST have normalized
> 3 to 5x ULN (confirmed by repeat testing)	Interrupt ACTEMRA dosing until < 3x ULN and follow recommendations above for >1 to 3x ULN For persistent increases > 3x ULN, discontinue ACTEMRA
> 5x ULN	Discontinue ACTEMRA

Low Absolute Neutrophil Count (ANC) ***[see Warnings and Precautions (5.3)]:***	
Lab Value (cells/mm^3)	**Recommendation**
ANC > 1000	Maintain dose
ANC 500 to 1000	Interrupt ACTEMRA dosing When ANC > 1000 cells/mm^3 resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
ANC < 500	Discontinue ACTEMRA

Low Platelet Count ***[see Warnings and Precautions (5.3)]:***	
Lab Value (cells/mm^3)	**Recommendation**
50,000 to 100,000	Interrupt ACTEMRA dosing When platelet count is > 100,000 cells/mm^3 resume ACTEMRA at 4 mg/kg and increase to 8 mg/kg as clinically appropriate
< 50,000	Discontinue ACTEMRA

3 DOSAGE FORMS AND STRENGTHS

Single-use vials of ACTEMRA (20 mg/mL):

- 80 mg/4 mL
- 200 mg/10 mL
- 400 mg/20 mL

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA for rheumatoid arthritis. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

ACTEMRA should not be administered in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:

- with chronic or recurrent infection;

- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants *[see Dosage and Administration (2.3), Adverse Reactions (6.1), and Patient Counseling Information (17.1)]*.

ACTEMRA should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Tuberculosis

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ACTEMRA.

Anti-tuberculosis therapy should also be considered prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

It is recommended that patients be screened for latent tuberculosis infection prior to starting ACTEMRA. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA.

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis. ACTEMRA should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation *[see Adverse Reactions (6.1)]*.

5.3 Laboratory Parameters

Neutrophils

Treatment with ACTEMRA was associated with a higher incidence of neutropenia. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

- It is not recommended to initiate ACTEMRA treatment in patients with a low neutrophil count i.e., absolute neutrophil count (ANC) $<2000/mm^3$. In patients who develop an absolute neutrophil count $<500/mm^3$ treatment is not recommended.

- Neutrophils should be monitored every 4 to 8 weeks *[see Clinical Pharmacology (12.2)]*. For recommended modifications based on ANC results *see Dosage and Administration (2.3)*.

Platelets

Treatment with ACTEMRA was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials *[see Adverse Reactions (6.1)]*.

- It is not recommended to initiate ACTEMRA treatment in patients with a platelet count below 100,000/mm^3. In patients who develop a platelet count <50,000/mm^3 treatment is not recommended.
- Platelets should be monitored every 4 to 8 weeks. For recommended modifications based on platelet counts *see Dosage and Administration (2.3)*.

Liver Function Tests

Treatment with ACTEMRA was associated with a higher incidence of transaminase elevations. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials *[see Adverse Reactions (6.1)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

In one case, a patient who had received ACTEMRA 8 mg/kg monotherapy without elevations in transaminases experienced elevation in AST to above 10x ULN and elevation in ALT to above 16x ULN when MTX was initiated in combination with ACTEMRA. Transaminases normalized when both treatments were held, but elevations recurred when MTX and ACTEMRA were restarted at lower doses. Elevations resolved when MTX and ACTEMRA were discontinued.

- It is not recommended to initiate ACTEMRA treatment in patients with elevated transaminases ALT or AST > 1.5x ULN. In patients who develop elevated ALT or AST > 5x ULN treatment is not recommended.
- ALT and AST levels should be monitored every 4 to 8 weeks. When clinically indicated, other liver function tests such as bilirubin should be considered. For recommended modifications based on transaminases *see Dosage and Administration (2.3)*.

Lipids

Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol *[see Adverse Reactions (6.1)]*.

- Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 6 month intervals.
- Patients should be managed according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

5.4 Immunosuppression

The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies *[see Adverse Reactions (6.1)]*. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

5.5 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in association with infusion of ACTEMRA *[see Adverse Reactions (6.1)]*. Appropriate medical treatment should be available for immediate use in the event of an anaphylactic reaction during administration of ACTEMRA.

5.6 Demyelinating Disorders

The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies. Patients should be

closely monitored for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

5.7 Active Hepatic Disease and Hepatic Impairment

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment *[see Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.

5.8 Vaccinations

Live vaccines should not be given concurrently with ACTEMRA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA. No data are available on the effectiveness of vaccination in patients receiving ACTEMRA. Because IL-6 inhibition may interfere with the normal immune response to new antigens, patients should be brought up to date on all recommended vaccinations, except for live vaccines, prior to initiation of therapy with ACTEMRA.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The ACTEMRA data described below includes 5 double-blind, controlled, multi-center studies. In these studies, patients received doses of ACTEMRA 8 mg/kg monotherapy (288 patients), ACTEMRA 8 mg/kg in combination with DMARDs (including methotrexate) (1582 patients), or ACTEMRA 4 mg/kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of ACTEMRA. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3296 for at least one year; 2806 received treatment for at least 2 years and 1222 for 3 years.

All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian.

6.1 Clinical Trials Experience

The most common serious adverse reactions were serious infections *[see Warnings and Precautions (5.1)]*. The most commonly reported adverse reactions in controlled studies up to 6 months (occurring in $\geq$ 5% of patients treated with ACTEMRA monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The proportion of patients who discontinued treatment due to any adverse reactions during the double-blind, placebo-controlled studies was 5% for patients taking ACTEMRA and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of ACTEMRA were increased hepatic transaminase values (per protocol requirement) and serious infections.

Overall Infections

In the 6-month, controlled clinical studies, the rate of infections in the ACTEMRA monotherapy group was 119 events per 100 patient-years and was similar in the methotrexate monotherapy group. The rate of infections in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD group was 133 and 127 events per 100 patient-years, respectively, compared to 112 events per 100 patient-years in the placebo plus DMARD group. The most commonly reported infections (5 to 8% of patients) were upper respiratory tract infections and nasopharyngitis.

The overall rate of infections with ACTEMRA in the all exposure population was 108 events per 100 patient-years.

Serious Infections

In the 6-month, controlled clinical studies, the rate of serious infections in the ACTEMRA monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD group was 4.4 and 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group.

In the all-exposure population, the overall rate of serious infections was 4.7 events per 100 patient-years. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. The overall rate of fatal serious infections was 0.13 per 100 patient-years. Cases of opportunistic infections have been reported *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Perforations

During the 6-month, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient years with ACTEMRA therapy.

In the all-exposure population, the overall rate of gastrointestinal perforation was 0.28 events per 100 patient-years. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate *[see Warnings and Precautions (5.2)]*. The relative contribution of these concomitant medications versus Actemra to the development of GI perforations is not known.

Infusion Reactions

In the 6-month, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event on the 4 mg/kg and 8 mg/kg dose during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1.0% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting.

Clinically significant hypersensitivity reactions (e.g., anaphylactoid and anaphylactic reactions) associated with ACTEMRA and requiring treatment discontinuation were reported 0.1% (3/2644) in the 6-month, controlled trials and in 0.2% (9/4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of ACTEMRA. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction *[see Warnings and Precautions (5.5)]*.

Laboratory Tests

Neutrophils

In the 6-month, controlled clinical studies, decreases in neutrophil counts below 1000/mm^3 occurred in 1.8% and 3.4% of patients in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000/mm^3 occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500/mm^3 occurred in 0.4% and 0.3% of patients in the 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000/mm^3 and the occurrence of serious infections.

In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 6-month controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Platelets

In the 6-month, controlled clinical studies, decreases in platelet counts below 100,000/mm^3 occurred in 1.3% and 1.7% of patients on 4 mg/kg and 8 mg/kg ACTEMRA plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

In the all-exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 6-month controlled clinical studies *[see Warnings and Precautions (5.3)]*.

Liver Function Tests

Liver enzyme abnormalities are summarized in **Table 1**. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of ACTEMRA, or reduction in ACTEMRA dose resulted in decrease or normalization of liver enzymes *[see Dosage and Administration (2.3)]*. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency *[see Warnings and Precautions (5.3)]*.

Table 1 Incidence of Liver Enzyme Abnormalities in the 6-Month Controlled Period of Studies I-V*

	ACTEMRA 8 mg/kg MONOTHERAPY N = 288 (%)	Methotrexate N = 284 (%)	ACTEMRA 4 mg/kg + DMARDs N = 774 (%)	ACTEMRA 8 mg/kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
AST (U/L)					
> ULN to 3x ULN	22	26	34	41	17
> 3x ULN to 5x ULN	0.3	2	1	2	0.3
> 5x ULN	0.7	0.4	0.1	0.2	< 0.1
ALT (U/L)					
> ULN to 3x ULN	36	33	45	48	23
> 3x ULN to 5x ULN	1	4	5	5	1
> 5x ULN	0.7	1	1.3	1.5	0.3

ULN = Upper Limit of Normal

*For a description of these studies, see Section 14, Clinical Studies.

Lipids

Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides), were first assessed at 6 weeks following initiation of ACTEMRA in the controlled 6-month clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg/dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

- Mean LDL increased by 13 mg/dL in the TCZ 4 mg/kg+DMARD arm, 20 mg/dL in the TCZ 8 mg/kg+DMARD, and 25 mg/dL in TCZ 8 mg/kg monotherapy.
- Mean HDL increased by 3 mg/dL in the TCZ 4 mg/kg+DMARD arm, 5 mg/dL in the TCZ 8 mg/kg+DMARD, and 4 mg/dL in TCZ 8 mg/kg monotherapy.
- Mean LDL/HDL ratio increased by an average of 0.14 in the TCZ 4 mg/kg+DMARD arm, 0.15 in the TCZ 8 mg/kg+DMARD, and 0.26 in TCZ 8 mg/kg monotherapy.
- ApoB/ApoA1 ratios were essentially unchanged in ACTEMRA-treated patients.

Elevated lipids responded to lipid lowering agents.

Immunogenicity

In the 6-month, controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty-six patients (2%) developed positive anti-tocilizumab antibodies, of whom 5 had an

associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies.

The data reflect the percentage of patients whose test results were positive for antibodies to tocilizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to tocilizumab with the incidence of antibodies to other products may be misleading.

Malignancies

During the 6-month, controlled period of the studies, 15 malignancies were diagnosed in patients receiving ACTEMRA, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years).

In the all-exposure population, the rate of malignancies remained consistent (1.10 events per 100 patient-years) with the rate observed in the 6-month, controlled period *[see Warnings and Precautions (5.4)]*.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 or 8 mg/kg ACTEMRA plus DMARD and at least 1% greater than that observed in patients on placebo plus DMARD are summarized in **Table 2.**

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 or 8 mg/kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

	6 Month Phase 3 Controlled Study Population				
Preferred Term	ACTEMRA 8 mg/kg MONOTHERAPY N = 288 (%)	Methotrexate N = 284 (%)	ACTEMRA 4 mg/kg + DMARDs N = 774 (%)	ACTEMRA 8 mg/kg + DMARDs N = 1582 (%)	Placebo + DMARDs N = 1170 (%)
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2
Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

7 DRUG INTERACTIONS

7.1 Other Drugs for Treatment of Rheumatoid Arthritis

Population pharmacokinetic analyses did not detect any effect of methotrexate, non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance.

Concomitant administration of a single dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure.

ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.1)]*.

7.2 Interactions with CYP450 Substrates

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CY2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effects on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28 % and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Prescribers should exercise caution when ACTEMRA is coadministered with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

7.3 Live Vaccines

Live vaccines should not be given concurrently with ACTEMRA *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. ACTEMRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

An embryo-fetal developmental toxicity study was performed in which pregnant cynomolgus monkeys were treated intravenously with tocilizumab (daily doses of 2, 10, or 50 mg/kg from gestation day 20-50) during organogenesis. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at 10 mg/kg and 50 mg/kg doses (1.25 and 6.25 times the human dose of 8 mg/kg every 4 weeks based on a mg/kg comparison).

Nonteratogenic Effects. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation until day 21 after delivery (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Pregnancy Registry: To monitor the outcomes of pregnant women exposed to ACTEMRA, a pregnancy registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

8.3 Nursing Mothers

It is not known whether tocilizumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ACTEMRA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of ACTEMRA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V *[see Clinical Studies (14)]*, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. The frequency of serious infection among ACTEMRA treated subjects 65 years of age and older was higher than those under the age of 65. As there is a higher incidence in infections in the elderly population in general, caution should be used when treating the elderly.

8.6 Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology *[see Warnings and Precautions (5.7)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild renal impairment. ACTEMRA has not been studied in patients with moderate to severe renal impairment *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

No studies on the potential for ACTEMRA to cause dependence have been performed. However, there is no evidence from the available data that ACTEMRA treatment results in dependence.

10 OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported in which a patient with multiple myeloma received a dose of 40 mg/kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg/kg, although all 5 patients at the highest dose of 28 mg/kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

11 DESCRIPTION

ACTEMRA (tocilizumab) is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa.

ACTEMRA is supplied as a sterile, preservative-free solution for intravenous (IV) infusion at a concentration of 20 mg/mL. ACTEMRA is a colorless to pale yellow liquid, with a pH of about 6.5. Single-use vials are available containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Injectable solutions of ACTEMRA are formulated in an aqueous solution containing disodium phosphate dodecahydrate and sodium dihydrogen phosphate dehydrate (as a 15 mmol/L phosphate buffer), polysorbate 80 (0.5 mg/ml), and sucrose (50 mg/mL).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

12.2 Pharmacodynamics

In clinical studies with the 4 mg/kg and 8 mg/kg doses of ACTEMRA, decreases in levels of C-reactive protein (CRP) to within normal ranges were seen as early as week 2. Changes in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate, serum amyloid A and increases in hemoglobin) with both doses, however the greatest improvements were observed with 8 mg/kg ACTEMRA.

In healthy subjects administered ACTEMRA in doses from 2 to 28 mg/kg, absolute neutrophil counts decreased to the nadir 3 to 5 days following ACTEMRA administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis patients demonstrated a similar pattern of absolute neutrophil counts following ACTEMRA administration *[see Warnings and Precautions (5.3)]*.

12.3 Pharmacokinetics

The pharmacokinetics characterized in healthy subjects and RA patients suggested that PK is similar between the two populations. The clearance (CL) of tocilizumab decreased with increased doses. At the 10 mg/kg single dose in RA patients, mean CL was 0.29 ± 0.10 mL/hr/kg and mean apparent terminal $t_{1/2}$ was 151 ± 59 hours (6.3 days).

The pharmacokinetics of tocilizumab were determined using a population pharmacokinetic analysis of 1793 rheumatoid arthritis patients treated with ACTEMRA 4 and 8 mg/kg every 4 weeks for 24 weeks.

The pharmacokinetic parameters of tocilizumab did not change with time. A more than dose-proportional increase in area under the curve (AUC) and trough concentration (C_{min}) was observed for doses of 4 and 8 mg/kg every 4 weeks. Maximum concentration (C_{max}) increased dose-proportionally. At steady-state, predicted AUC and C_{min} were 2.7 and 6.5-fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

For doses of ACTEMRA 4 mg/kg given every 4 weeks, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 13000 ± 5800 mcg•h/mL, 1.49 ± 2.13 mcg/mL, and 88.3 ± 41.4 mcg/mL, respectively. The accumulation ratios for AUC and C_{max} were 1.11 and 1.02, respectively. The accumulation ratio was higher for C_{min} (1.96). Steady-state was reached following the first administration for C_{max} and AUC, respectively, and after 16 weeks C_{min}.

For doses of ACTEMRA 8 mg/kg given every 4 weeks, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 35000 ± 15500 mcg•h/mL, 9.74 ± 10.5 mcg/mL, and 183 ± 85.6 mcg/mL, respectively. The accumulation ratios for AUC and C_{max} were 1.22 and 1.06, respectively. The accumulation ratio was higher for C_{min} (2.35). Steady-state was reached following the first administration and after 8 and 20 weeks for C_{max}, AUC, and C_{min}, respectively. Tocilizumab AUC, C_{min} and C_{max} increased with increase of body weight. At body weight ≥ 100 kg, the predicted mean (± SD) steady-state AUC, C_{min} and C_{max} of tocilizumab were 55500 ± 14100 mcg•h/mL, 19.0 ± 12.0 mcg/mL, and 269 ± 57 mcg/mL, respectively, which are higher than mean exposure values for the patient population. Therefore, ACTEMRA doses exceeding 800 mg per infusion are not recommended *[see Dosage and Administration (2.1)]*.

Distribution

Following intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. In rheumatoid arthritis patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

Elimination

The total clearance of tocilizumab is concentration-dependent and is the sum of the linear clearance and the nonlinear clearance. The linear clearance was estimated to be 12.5 mL/h in the population pharmacokinetic analysis. The concentration-dependent nonlinear clearance plays a major role at low tocilizumab concentrations. Once the nonlinear clearance pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance.

The $t_{1/2}$ of tocilizumab is concentration-dependent. The concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg/kg and up to 13 days for 8 mg/kg every 4 weeks at steady-state.

Pharmacokinetics in Special Populations

Population pharmacokinetic analyses in adult rheumatoid arthritis patients showed that age, gender and race did not affect the pharmacokinetics of tocilizumab. Linear clearance was found to increase with body size. The body weight-based dose (8 mg/kg) resulted in approximately 86% higher exposure in patients who are greater than 100 kg in comparison to patients who are less than 60 kg.

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.

Most patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (creatinine clearance < 80 mL/min and ≥ 50 mL/min based on Cockcroft-Gault) did not impact the pharmacokinetics of tocilizumab. No dose adjustment is required in patients with mild renal impairment.

Drug Interactions

In vitro data suggested that IL-6 reduced mRNA expression for several CYP450 isoenzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and this reduced expression was reversed by co-incubation with tocilizumab at clinically relevant concentrations. Accordingly, inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. Its effect on CYP2C8 or transporters (e.g., P-gp) is unknown. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Caution should be exercised when ACTEMRA is coadministered with drugs where decrease in effectiveness is undesirable, e.g. oral contraceptives (CYP3A4 substrates). *[see Drug Interactions (7.2)]*.

Simvastatin

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 12 RA patients, not treated with ACTEMRA, receiving 40 mg simvastatin, exposures of simvastatin and its metabolite, simvastatin acid, was 4- to 10-fold and 2-fold higher, respectively, than the exposures observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (10 mg/kg), exposure of simvastatin and simvastatin acid decreased by 57% and 39%, respectively, to exposures that were similar or slightly higher than those observed in healthy subjects. Exposures of simvastatin and simvastatin acid increased upon withdrawal of ACTEMRA in RA patients. Selection of a particular dose of simvastatin in RA patients should take into account the potentially lower exposures that may result after initiation of ACTEMRA (due to normalization of CYP3A4) or higher exposures after discontinuation of ACTEMRA.

Omeprazole

Omeprazole is a CYP2C19 and CYP3A4 substrate. In RA patients receiving 10 mg omeprazole, exposure to omeprazole was approximately 2 fold higher than that observed in healthy subjects. In RA patients receiving 10 mg omeprazole, before and one week after ACTEMRA infusion (8 mg/kg), the omeprazole AUC_{inf} decreased by 12% for poor (N=5) and intermediate metabolizers (N=5) and by 28% for extensive metabolizers (N=8) and were slightly higher than those observed in healthy subjects.

Dextromethorphan

Dextromethorphan is a CYP2D6 and CYP3A4 substrate. In 13 RA patients receiving 30 mg dextromethorphan, exposure to dextromethorphan was comparable to that in healthy subjects. However, exposure to its metabolite, dextrorphan (a CYP3A4 substrate), was a fraction of that observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (8 mg/kg), dextromethorphan exposure was decreased by approximately 5%. However, a larger decrease (29%) in dextrorphan levels was noted after ACTEMRA infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis. No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab.

Mutagenesis. Tocilizumab was negative in the in vitro Ames bacterial reverse mutation assay and the in vitro chromosomal aberrations assay using human peripheral blood lymphocytes.

Impairment of Fertility. Fertility studies conducted in male and female mice using a murine analogue of tocilizumab showed no impairment of fertility.

14 CLINICAL STUDIES

The efficacy and safety of ACTEMRA was assessed in five randomized, double-blind, multicenter studies in patients > 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. ACTEMRA was given intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II and III) or other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV) in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonists (Study V).

Study I evaluated patients with moderate to severe active rheumatoid arthritis who had not been treated with MTX within 6 months prior to randomization, or who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had rheumatoid arthritis < 2 years. Patients received ACTEMRA 8 mg/kg monotherapy or MTX alone (dose titrated over 8 weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of ACTEMRA patients who achieved an ACR20 response at Week 24.

Study II is an ongoing 2-year study with a planned interim analysis at week 24 that evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg/kg, ACTEMRA 4 mg/kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint at week 24 was the proportion of patients who achieved an ACR20 response.

Study III evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg/kg, ACTEMRA 4 mg/kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study IV evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received ACTEMRA 8 mg/kg or placebo every four weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Study V evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomization. Patients received ACTEMRA 8 mg/kg, ACTEMRA 4 mg/kg, or placebo

every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24.

Clinical Response

The percentages of ACTEMRA-treated patients achieving ACR20, 50 and 70 responses are shown in **Table 3.** In all studies, patients treated with 8 mg/kg ACTEMRA had statistically significant ACR20, ACR50, and ACR70 response rates versus MTX- or placebo-treated patients at week 24.

Patients treated with ACTEMRA at a dose of 4 mg/kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with ACTEMRA 8 mg/kg.

Table 3 ACR Response at 6 Months in Active and Placebo Controlled Trials (Percent of Patients)

Percent of Patients													
	Study I		Study II			Study III			Study IV		Study V		
Response Rate Week 24	MTX N=284	ACTEMRA 8 mg/kg N=286	Placebo + MTX N=393	ACTEMRA 4 mg/kg + MTX N=399	ACTEMRA 8 mg/kg + MTX N=398	Placebo + MTX N=204	ACTEMRA 4 mg/kg + MTX N=213	ACTEMRA 8 mg/kg + MTX N=205	Placebo + DMARDs N=413	ACTEMRA 8 mg/kg + DMARDs N=803	Placebo + MTX N=158	ACTEMRA 4 mg/kg + MTX N=161	ACTEMRA 8 mg/kg + MTX N=170
ACR20													
Responders	53%	70%	27%	51%	56%	27%	48%	59%	25%	61%	10%	30%	50%
Weighted Difference %[a]		19		23	29		23	32		35		25	46
(95% CI)[b]		(11, 27)		(17, 29)	(23, 35)		(15, 32)	(23, 41)		(30, 40)		(15, 36)	(36, 56)
ACR50													
Responders	34%	44%	10%	25%	32%	11%	32%	44%	9%	38%	4%	17%	29%
Weighted Difference %[a]		12		15	22		21	33		28		15	31
(95% CI)[b]		(4, 20)		(9, 20)	(16, 28)		(13, 29)	(25, 41)		(23, 33)		(5, 25)	(21, 41)
ACR70													
Responders	15%	28%	2%	11%	13%	2%	12%	22%	3%	21%	1%	5%	12%
Weighted Difference %[a]		14		8	10		11	20		17		4	12
(95% CI)[b]		(7, 22)		(3, 13)	(5, 15)		(4, 18)	(12, 27)		(13, 21)		(-6, 13)	(3, 22)

[a] The weighted difference is the difference between ACTEMRA and Placebo response rates, adjusted for site (and disease duration for Study I only).

[b] CI: 95% confidence interval of the weighted difference

The results of the components of the ACR response criteria for Studies III and V are shown in **Table 4**. Similar results to Study III were observed in Studies I, II and IV.

Table 4 Components of ACR Response at 6 Months

	Study III						Study V					
	ACTEMRA 4 mg/kg + MTX N=213		ACTEMRA 8 mg/kg + MTX N=205		Placebo + MTX N=204		ACTEMRA 4 mg/kg + MTX N=161		ACTEMRA 8 mg/kg + MTX N=170		Placebo + MTX N=158	
Component (mean)	Baseline	Week 24[a]	Baseline	Week 24[a]	Baseline	Week 24	Baseline	Week 24[a]	Baseline	Week 24[a]	Baseline	Week 24
Number of tender joints (0-68)	33	19 -7.0 (-10.0, -4.1)	32	14.5 -9.6 (-12.6, -6.7)	33	25	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
Number of swollen joints (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
Pain[b]	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
Patient global assessment[b]	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45	70	46 -10.0 (-20.3, 0.3)	70	36 -17.4 (-27.8, -7.0)	71	51
Physician global assessment[b]	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
Disability index (HAQ)[c]	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg/dL)	2.79	1.17 -1.30 (-2.0, -0.59)	2.61	0.25 -2.156 (-2.86, -1.46)	2.36	1.89	3.11	1.77 -1.34 (-2.5, -0.15)	2.80	0.28 -2.52 (-3.72, -1.32)	3.705	3.06

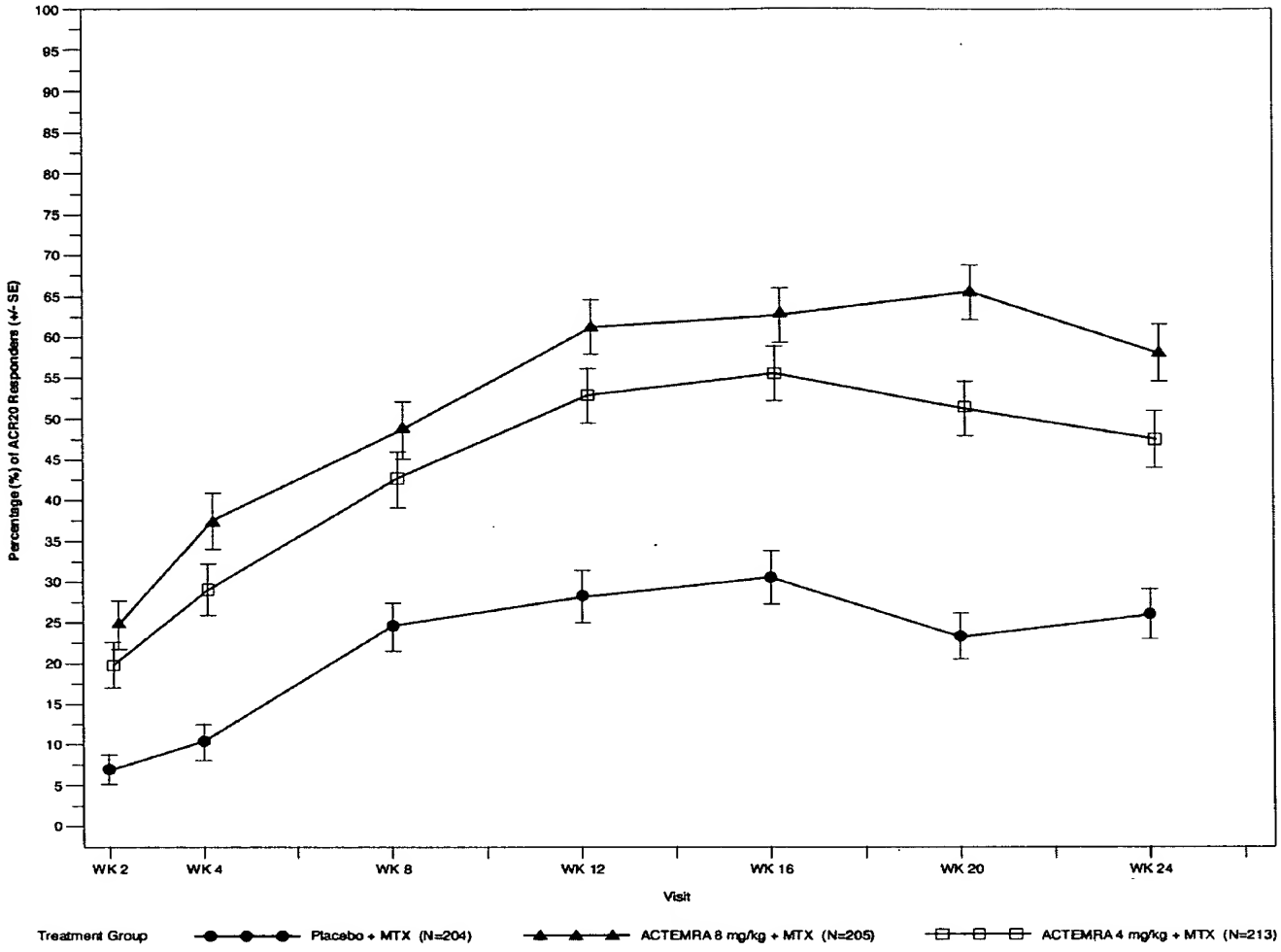
[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

[b] Visual analog scale: 0 = best, 100 = worst

[c] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

The percent of ACR20 responders by visit for Study III is shown in **Figure 1**. Similar responses were observed in studies I, II, IV, and V.

Figure 1 **Percent of ACR20 Responders by Visit for Study III (Inadequate Response to MTX)***



*The same patients may not have responded at each timepoint.

16 HOW SUPPLIED/STORAGE AND HANDLING

ACTEMRA (tocilizumab) is supplied in single-use vials as a preservative-free, sterile concentrate (20 mg/mL) solution for intravenous infusion. The following packaging configurations are available:

Individually packaged, single-use vials:

NDC 50242-135-01 providing 80 mg/4 mL

NDC 50242-136-01 providing 200 mg/10 mL

NDC 50242-137-01 providing 400 mg/20 mL

Box of 4 single-use vials:

NDC 50242-135-04 providing 80 mg/4 mL

NDC 50242-136-04 providing 200 mg/10 mL

NDC 50242-137-04 providing 400 mg/20 mL

Storage and Stability: Do not use beyond expiration date on the container. ACTEMRA must be refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect the vials from light by storage in the original package until time of use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

17 PATIENT COUNSELING INFORMATION

17.1 Patient Counseling

Patients should be advised of the potential benefits and risks of ACTEMRA. Physicians should instruct their patients to read the Medication Guide before starting ACTEMRA therapy.

- **Infections:**
  Inform patients that ACTEMRA may lower their resistance to infections. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.
- **Gastrointestinal Perforation:**
  Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines. Instruct the patient of the importance of contacting their doctor immediately when symptoms of severe, persistent abdominal pain appear to assure rapid evaluation and appropriate treatment.

17.2 Medication Guide

MEDICATION GUIDE

ACTEMRA® (AC-TEM-RA)

(tocilizumab)

Read this Medication Guide before you start ACTEMRA and before each infusion. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about ACTEMRA?

ACTEMRA can cause serious side effects including:

1. Serious Infections

ACTEMRA is a medicine that affects your immune system. ACTEMRA can lower the ability of your immune system to fight infections. Some people have serious infections while taking ACTEMRA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your doctor should test you for TB before starting ACTEMRA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with ACTEMRA.

You should not start taking ACTEMRA if you have any kind of infection unless your healthcare provider says it is okay.

Before starting ACTEMRA, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweating, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss

- warm, red, or painful skin or sores on your body
- diarrhea or stomach pain
- burning when you urinate or urinating more often than normal
- feel very tired

- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidiomycosis, or blastomycosis). These infections may happen or become more severe if you use ACTEMRA. Ask your healthcare provider, if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.

After starting ACTEMRA, call your healthcare provider right away if you have any symptoms of an infection. ACTEMRA can make you more likely to get infections or make worse any infection that you have.

2. **Tears (perforation) of the stomach or intestines.**

   - Before taking ACTEMRA, tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking ACTEMRA get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
   - Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

3. **Changes in certain laboratory test results.** Your healthcare provider should do blood tests before you start receiving ACTEMRA and every 4 to 8 weeks during treatment to check for the following side effects of ACTEMRA:

   - **low neutrophil count**. Neutrophils are white blood cells that help the body fight off bacterial infections.
   - **low platelet count**. Platelets are blood cells that help with blood clotting and stop bleeding.
   - **increase in certain liver function tests**.

   You should not receive ACTEMRA if your neutrophil or platelet counts are too low or your liver function tests are too high.

   Your healthcare provider may stop your ACTEMRA treatment for a period of time or change your dose of medicine if needed because of changes in these blood test results.

   You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving ACTEMRA, and then every 6 months after that. Normal cholesterol levels are important to good heart health.

4. **Cancer.**

ACTEMRA may decrease the activity of your immune system. Medicines that affect the immune system may increase your risk of certain cancers. Tell your healthcare provider if you have ever had any type of cancer.

See "What are the possible side effects with ACTEMRA?" for more information about side effects.

What is ACTEMRA?

ACTEMRA is a prescription medicine called an Interleukin-6 (IL-6) receptor inhibitor. ACTEMRA is used to treat adults with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well.

It is not known if ACTEMRA is safe and effective in children.

What should I tell my healthcare provider before receiving ACTEMRA?

ACTEMRA may not be right for you. Before starting ACTEMRA, tell your healthcare provider if you:

- have an infection. See "What is the most important information I should know about ACTEMRA?"
- have liver problems
- have any stomach-area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have or had a condition that affects your nervous system, such as multiple sclerosis
- have recently received or are scheduled to receive a vaccine. People who take ACTEMRA should not receive live vaccines. People taking ACTEMRA can receive non-live vaccines
- plan to have surgery or a medical procedure
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if ACTEMRA will harm your unborn baby.

Pregnancy Registry: Genentech has a registry for pregnant women who take ACTEMRA. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking ACTEMRA, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.

- plan to breast-feed or are breast-feeding. You and your healthcare provider should decide if you will take ACTEMRA or breast-feed. You should not do both.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. ACTEMRA and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your RA. You should not take etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), or golimumab (Simponi®), while you are taking ACTEMRA. Taking ACTEMRA with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask you healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ACTEMRA?

- You will receive ACTEMRA from a healthcare provider through a needle placed in a vein in your arm (IV or intravenous infusion). The infusion will take about 1 hour to give you the full dose of medicine.
- You will receive a dose of ACTEMRA about every 4 weeks.
- If you miss a scheduled dose of ACTEMRA, ask your healthcare provider when to schedule your next infusion.

- While taking ACTEMRA, you may continue to use other medicines that help treat your rheumatoid arthritis such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as instructed by your healthcare provider.
- Keep all of your follow-up appointments and get your blood tests as ordered by your healthcare provider.

What are the possible side effects with ACTEMRA?

ACTEMRA can cause serious side effects, including:

- See "What is the most important information I should know about ACTEMRA?"
- **Hepatitis B infection in people who carry the virus in their blood.** If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus may become active while you use ACTEMRA. This happens with other biologic medicines used to treat RA. Your doctor may do blood tests before you start treatment with ACTEMRA and while you are using ACTEMRA. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B infection:
  - feel very tired
  - skin or eyes look yellow
  - little or no appetite
  - vomiting
  - clay-colored bowel movements
  - fevers
  - chills
  - stomach discomfort
  - muscle aches
  - dark urine
  - skin rash
- **Nervous system problems**. Multiple Sclerosis has been diagnosed rarely in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.
- **Allergic Reactions.** Serious allergic reactions can happen with ACTEMRA. These reactions may not happen with your first infusion, and may happen with future infusions of ACTEMRA. Tell your healthcare provider right away if you have any of the following signs of a serious allergic reaction:
  - shortness of breath or trouble breathing
  - skin rash
  - swelling of the lips, tongue, or face
  - chest pain
  - feeling dizzy or faint

Common side effects of ACTEMRA include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- increased blood pressure (hypertension)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of ACTEMRA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Genentech at 1-888-835-2555.

General information about ACTEMRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about ACTEMRA.

If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about ACTEMRA that is written for health professionals.

For more information, go to www.ACTEMRA.com or call 1-800-ACTEMRA.

What are the ingredients in ACTEMRA?

Active ingredient: tocilizumab

Inactive ingredients: sucrose, polysorbate 80, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

ACTEMRA is a registered trademark of Chugai Seiyaku Kabushiki Kaisha Corp., a member of the Roche Group.

Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
US License No.1048

PI Issued: Month Year

EXHIBIT 5
RHEUMATOID ARTHRITIS
TRANSLATION EXPLANATION

薬食審査発０７０３第１０号
薬食安発０７０３第１０号
平成２１年７月３日

都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長

厚生労働省医薬食品局安全対策課長

医薬品の効能又は効果等における「関節リウマチ」の呼称の取扱いについて

「慢性関節リウマチ」については、平成17年7月の社会保障審議会の答申を経て、同年10月の総務省告示第1147号により疾病、傷害及び死因分類が医学の進歩等への対応として「関節リウマチ」に改正されたこと、本年6月に日本リウマチ学会から要望があったこと等を踏まえ、今般、薬事法上の承認に係る医薬品の効能又は効果、添付文書等における記載等に関し、「関節リウマチ」の呼称の使用を促進する観点から、下記のとおり取り扱うこととしましたので、貴管下関係業者等に対し周知徹底方御配慮願います。

記

１．薬事法上の承認に係る医薬品の効能又は効果の「慢性関節リウマチ」から「関節リウマチ」への変更は、一部変更承認申請により行うこと。なお、他の事由により一部変更承認申請を行う機会等にあわせて行うことでも差し支えないこと。

２．　上記１．の申請の有無にかかわらず、「慢性関節リウマチ」を効能又は効果にもつ医薬品の添付文書等における「慢性関節リウマチ」の記載は、「関節リウマチ」へ記載を変更するよう努めること。

PFE0703-10

PFS0703-10

July 3, 2009

To: Those in Charge of Health in
Prefectural Governments

Subject: "Rheumatoid Arthritis" as Used in Drug Indications

Be it known, that it has been decided that the use of the term "Rheumatoid Arthritis" will be handled as described below to encourage use of the term "Rheumatoid Arthritis" instead of "Chronic Rheumatoid Arthritis" in drug indications and package inserts, for which approval is required as provided for by the Pharmaceutical Affairs Law.

The decision has been made due to the fact that the term "Chronic Rheumatoid Arthritis" is replaced by "Rheumatoid Arthritis" as stated in Notification No.1147 of the Ministry of Internal Affairs and Telecommunications of October 2005 as part of modifications in classification of illnesses, injuries and death causes in response to advances in medicine, on the basis of a report submitted by the Social Security Council in July 2005. Consideration has also been given to the request for the change of the term from Japan College of Rheumatology.

Accordingly, please take steps to make all business entities and those concerned in your jurisdiction fully informed about the above decision.

Note

1. Replacement of the term "Chronic Rheumatoid Arthritis" by the term "Rheumatoid Arthritis" in drug indications, for which approval is required in accordance with the Pharmaceutical Affairs Law, shall be made by applying for a partial amendment of indications. In this case, the aforesaid application may be made concurrently when an application is filed for a partial amendment for other reasons.

2. Efforts are to be made to replace "Chronic Rheumatoid Arthritis" by "Rheumatoid Arthritis" in cases where certain drugs are indicated for "Chronic Rheumatoid Arthritis" in package inserts or other prescribing information about said drugs, regardless of whether the application mentioned in the foregoing paragraph has been filed or not.

Director of Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Director of Safety Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

EXHIBIT 6
SIGNIFICANT MARKETING ACTIVITIES AND DATES

EXHIBIT 6

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY THE MARKETING APPLICANT DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES.

Record Date (dd-mon-yyyy)	Description of Activity
01-Oct-2004	Original IND Submission
05-Oct-2004	**FDA Confirmation of IND Submission (per FDA letter dated October 14, 2004)**
07-Oct-2004	General Correspondence
08-Oct-2004	General Correspondence
14-Oct-2004	General Correspondence
15-Oct-2004	General Correspondence
04-Nov-2004	**IND Effective Date (i.e., 30 days from FDA confirmation of IND submission)**
05-Nov-2004	General Correspondence
12-Nov-2004	Information Amendments
03-Dec-2004	Information Amendments
07-Dec-2004	Information Amendments
16-Dec-2004	Safety Report
16-Dec-2004	Protocol Amendments
21-Dec-2004	Protocol Amendments

31-Dec-2004	Safety Report
03-Jan-2005	Safety Report
05-Jan-2005	Protocol Amendments
05-Jan-2005	Protocol Amendments
07-Jan-2005	Safety Report
07-Jan-2005	Protocol Amendments
11-Jan-2005	Safety Report
14-Jan-2005	General Correspondence
17-Jan-2005	Protocol Amendments
17-Jan-2005	Safety Report
24-Jan-2005	Information Amendments
27-Jan-2005	General Correspondence
28-Jan-2005	Safety Report
28-Jan-2005	General Correspondence
31-Jan-2005	General Correspondence
01-Feb-2005	Protocol Amendments
01-Feb-2005	Safety Report
04-Feb-2005	General Correspondence
07-Feb-2005	Protocol Amendments

07-Feb-2005	Protocol Amendments
14-Feb-2005	Protocol Amendments
14-Feb-2005	Protocol Amendments
14-Feb-2005	General Correspondence
15-Feb-2005	General Correspondence
16-Feb-2005	Protocol Amendments
18-Feb-2005	Protocol Amendments
22-Feb-2005	Protocol Amendments
25-Feb-2005	Safety Report
28-Feb-2005	Safety Report
01-Mar-2005	General Correspondence
02-Mar-2005	General Correspondence
03-Mar-2005	General Correspondence
04-Mar-2005	Safety Report
11-Mar-2005	Information Amendments
14-Mar-2005	Protocol Amendments
18-Mar-2005	Safety Report
18-Mar-2005	General Correspondence
21-Mar-2005	Protocol Amendments

22-Mar-2005	Protocol Amendments
24-Mar-2005	Safety Report
24-Mar-2005	Protocol Amendments
29-Mar-2005	Protocol Amendments
18-Apr-2005	Protocol Amendments
19-Apr-2005	Safety Report
26-Apr-2005	Safety Report
28-Apr-2005	Protocol Amendments
06-May-2005	Information Amendments
10-May-2005	Protocol Amendments
20-May-2005	Protocol Amendments
26-May-2005	General Correspondence
27-May-2005	Safety Report
01-Jun-2005	Protocol Amendments
06-Jun-2005	Information Amendments
06-Jun-2005	Protocol Amendments
07-Jun-2005	Safety Report
16-Jun-2005	Safety Report
16-Jun-2005	General Correspondence

21-Jun-2005	Protocol Amendments
21-Jun-2005	Safety Report
28-Jun-2005	Information Amendment
29-Jun-2005	Safety Report
30-Jun-2005	Safety Report
01-Jul-2005	Protocol Amendments
11-Jul-2005	Safety Report
13-Jul-2005	Safety Report
15-Jul-2005	Protocol Amendments
15-Jul-2005	Protocol Amendments
20-Jul-2005	Safety Report
27-Jul-2005	Protocol Amendments
28-Jul-2005	Protocol Amendments
05-Aug-2005	Safety Report
12-Aug-2005	Safety Report
15-Aug-2005	Protocol Amendments
19-Aug-2005	Protocol Amendments
19-Aug-2005	Safety Report
26-Aug-2005	Safety Report

26-Aug-2005	General Correspondence
02-Sep-2005	Protocol Amendments
02-Sep-2005	Safety Report
08-Sep-2005	General Correspondence
12-Sep-2005	Safety Report
02-Sep-2005	Information Amendment
19-Sep-2005	Protocol Amendments
19-Sep-2005	Information Amendment
21-Sep-2005	General Correspondence
22-Sep-2005	General Correspondence
28-Sep-2005	General Correspondence
28-Sep-2005	Safety Report
30-Sep-2005	Protocol Amendments
30-Sep-2005	Safety Report
30-Sep-2005	Information Amendments
04-Oct-2005	Safety Report
05-Oct-2005	Safety Report
06-Oct-2005	Protocol Amendments
07-Oct-2005	Protocol Amendments

14-Oct-2005	Safety Report
18-Oct-2005	Protocol Amendments
21-Oct-2005	Safety Report
24-Oct-2005	Safety Report
25-Oct-2005	Safety Report
26-Oct-2005	Protocol Amendments
27-Oct-2005	Safety Report
28-Oct-2005	Safety Report
03-Nov-2005	Safety Report
09-Nov-2005	Protocol Amendments
10-Nov-2005	General Correspondence
11-Nov-2005	Safety Report
17-Nov-2005	Protocol Amendments
17-Nov-2005	Safety Report
18-Nov-2005	Safety Report
22-Nov-2005	Protocol Amendments
22-Nov-2005	Safety Report
23-Nov-2005	Protocol Amendments
23-Nov-2005	Annual Report

23-Nov-2005	Safety Report
28-Nov-2005	Safety Report
01-Dec-2005	Safety Report
06-Dec-2005	Information Amendments
06-Dec-2005	Safety Report
07-Dec-2005	Safety Report
09-Dec-2005	Protocol Amendments
12-Dec-2005	General Correspondence
15-Dec-2005	Safety Report
21-Dec-2005	Safety Report
22-Dec-2005	Protocol Amendments
22-Dec-2005	Safety Report
23-Dec-2005	Protocol Amendments
23-Dec-2005	Safety Report
29-Dec-2005	Safety Report
02-Jan-2006	Safety Report
03-Jan-2006	Safety Report
06-Jan-2006	Information Amendments
06-Jan-2006	Safety Report

09-Jan-2006	Safety Report
12-Jan-2006	Safety Report
18-Jan-2006	Safety Report
20-Jan-2006	Safety Report
23-Jan-2006	Protocol Amendments
30-Jan-2006	Protocol Amendments
31-Jan-2006	Safety Report
01-Feb-2006	Safety Report
03-Feb-2006	Safety Report
07-Feb-2006	Safety Report
09-Feb-2006	Safety Report
15-Feb-2006	Protocol Amendments
17-Feb-2006	Safety Report
23-Feb-2006	Safety Report
27-Feb-2006	Safety Report
28-Feb-2006	Protocol Amendments
28-Feb-2006	Annual Report
03-Mar-2006	Safety Reports
09-Mar-2006	Safety Reports

10-Mar-2006	Safety Reports
14-Mar-2006	Safety Reports
16-Mar-2006	Safety Reports
17-Mar-2006	Safety Reports
20-Mar-2006	Protocol Amendments
21-Mar-2006	Safety Reports
22-Mar-2006	Safety Reports
27-Mar-2006	Protocol Amendments
29-Mar-2006	Safety Reports
30-Mar-2006	Safety Reports
04-Apr-2006	Safety Reports
05-Apr-2006	Safety Reports
11-Apr-2006	Safety Reports
13-Apr-2006	Safety Reports
18-Apr-2006	General Correspondence
20-Apr-2006	Safety Reports
21-Apr-2006	Protocol Amendments
21-Apr-2006	Safety Reports
25-Apr-2006	Safety Reports

26-Apr-2006	Safety Reports
27-Apr-2006	Safety Reports
28-Apr-2006	Safety Reports
02-May-2006	Safety Reports
05-May-2006	Safety Reports
05-May-2006	General Correspondence
08-May-2006	Protocol Amendments
09-May-2006	Protocol Amendments
11-May-2006	Safety Reports
12-May-2006	Safety Reports
16-May-2006	Protocol Amendments
23-May-2006	Safety Reports
25-May-2006	Safety Reports
30-May-2006	General Correspondence
02-Jun-2006	Information Amendments
02-Jun-2006	Safety Reports
06-Jun-2006	Protocol Amendments
07-Jun-2006	General Correspondence
08-Jun-2006	Safety Reports

08-Jun-2006	Information Amendments
14-Jun-2006	Protocol Amendments
14-Jun-2006	Safety Reports
15-Jun-2006	Protocol Amendments
15-Jun-2006	Information Amendments
16-Jun-2006	Safety Reports
20-Jun-2006	Safety Reports
22-Jun-2006	Safety Reports
28-Jun-2006	Safety Reports
29-Jun-2006	Safety Reports
30-Jun-2006	Protocol Amendments
30-Jun-2006	Safety Reports
30-Jun-2006	Information Amendments
06-Jul-2006	Safety Reports
06-Jul-2006	Information Amendments
07-Jul-2006	Safety Reports
14-Jul-2006	Safety Reports
21-Jul-2006	Protocol Amendments
21-Jul-2006	Safety Reports

25-Jul-2006	Safety Reports
28-Jul-2006	Protocol Amendments
01-Aug-2006	General Correspondence
01-Aug-2006	Information Amendments
03-Aug-2006	Safety Reports
04-Aug-2006	Information Amendments
04-Aug-2006	Safety Reports
09-Aug-2006	Safety Reports
17-Aug-2006	Safety Reports
18-Aug-2006	Safety Reports
21-Aug-2006	Protocol Amendments
23-Aug-2006	Safety Reports
24-Aug-2006	Safety Reports
24-Aug-2006	Information Amendments
29-Aug-2006	Protocol Amendments
29-Aug-2006	Safety Reports
30-Aug-2006	Safety Reports
31-Aug-2006	Safety Reports
01-Sep-2006	Safety Reports

01-Sep-2006	Information Amendments
01-Sep-2006	General Correspondence
07-Sep-2006	Safety Reports
13-Sep-2006	Safety Reports
15-Sep-2006	Safety Reports
20-Sep-2006	General Correspondence
21-Sep-2006	Safety Reports
27-Sep-2006	Protocol Amendments
27-Sep-2006	Safety Reports
29-Sep-2006	Safety Reports
05-Oct-2006	Safety Reports
06-Oct-2006	Safety Reports
06-Oct-2006	Protocol Amendments
11-Oct-2006	Safety Reports
13-Oct-2006	Safety Reports
19-Oct-2006	Safety Reports
23-Oct-2006	Protocol Amendments
25-Oct-2006	Safety Reports
25-Oct-2006	General Correspondence

26-Oct-2006	Safety Reports
27-Oct-2006	Safety Reports
31-Oct-2006	Safety Reports
01-Nov-2006	Information Amendments
03-Nov-2006	General Correspondence
07-Nov-2006	Safety Reports
08-Nov-2006	Safety Reports
08-Nov-2006	Safety Reports
09-Nov-2006	Safety Reports
09-Nov-2006	General Correspondence
10-Nov-2006	Safety Reports
14-Nov-2006	Safety Reports
17-Nov-2006	Safety Reports
21-Nov-2006	Safety Reports
21-Nov-2006	Annual Reports
28-Nov-2006	Meeting Request
29-Nov-2006	Safety Reports
29-Nov-2006	Safety Reports
29-Nov-2006	General Correspondence

05-Dec-2006	Safety Reports
07-Dec-2006	Protocol Amendments
08-Dec-2006	Safety Reports
13-Dec-2006	Safety Reports
14-Dec-2006	General Correspondence
19-Dec-2006	Information Amendments
20-Dec-2006	Safety Reports
21-Dec-2006	General Correspondence
22-Dec-2006	Safety Reports
02-Jan-2007	Safety Reports
04-Jan-2007	Safety Reports
05-Jan-2007	Safety Reports
05-Jan-2007	General Correspondence
07-Jan-2007	General Correspondence
17-Jan-2007	Safety Reports
18-Jan-2007	Protocol Amendments
18-Jan-2007	General Correspondence
19-Jan-2007	Safety Reports
22-Jan-2007	General Correspondence

24-Jan-2007	Safety Reports
24-Jan-2007	General Correspondence
25-Jan-2007	Protocol Amendments
26-Jan-2007	Safety Reports
29-Jan-2007	Protocol Amendments
31-Jan-2007	Safety Reports
01-Feb-2007	Safety Reports
02-Feb-2007	General Correspondence
05-Feb-2007	Safety Reports
05-Feb-2007	General Correspondence
06-Feb-2007	General Correspondence
07-Feb-2007	Safety Reports
09-Feb-2007	Information Amendments
12-Feb-2007	General Correspondence
13-Feb-2007	Safety Reports
19-Feb-2007	General Correspondence
26-Feb-2007	Safety Reports
27-Feb-2007	Information Amendments
28-Feb-2007	Safety Reports

06-Mar-2007	Safety Reports
13-Mar-2007	Information Amendments
14-Mar-2007	Protocol Amendments
14-Mar-2007	Safety Reports
14-Mar-2007	Information Amendments
15-Mar-2007	General Correspondence
20-Mar-2007	Safety Reports
20-Mar-2007	Information Amendments
30-Mar-2007	Safety Reports
03-Apr-2007	Safety Reports
05-Apr-2007	Safety Reports
05-Apr-2007	General Correspondence
06-Apr-2007	Information Amendments
06-Apr-2007	General Correspondence
10-Apr-2007	Safety Reports
12-Apr-2007	Safety Reports
18-Apr-2007	Safety Reports
18-Apr-2007	General Correspondence
19-Apr-2007	Safety Reports

20-Apr-2007	General Correspondence
23-Apr-2007	Safety Reports
23-Apr-2007	General Correspondence
26-Apr-2007	Safety Reports
26-Apr-2007	General Correspondence
02-May-2007	Safety Reports
02-May-2007	General Correspondence
03-May-2007	Safety Reports
04-May-2007	General Correspondence
04-May-2007	Safety Reports
09-May-2007	Safety Reports
11-May-2007	Safety Reports
14-May-2007	Safety Reports
15-May-2007	Protocol Amendments
15-May-2007	General Correspondence
15-May-2007	Information Amendment
17-May-2007	Safety Reports
18-May-2007	Safety Reports
29-May-2007	Safety Reports

29-May-2007	General Correspondence
30-May-2007	Safety Reports
30-May-2007	General Correspondence
31-May-2007	General Correspondence
04-Jun-2007	Safety Reports
07-Jun-2007	Safety Reports
12-Jun-2007	Safety Reports
19-Jun-2007	Protocol Amendments
19-Jun-2007	General Correspondence
20-Jun-2007	Safety Reports
21-Jun-2007	Safety Reports
26-Jun-2007	Meeting Request
26-Jun-2007	General Correspondence
27-Jun-2007	Safety Reports
27-Jun-2007	General Correspondence
27-Jun-2007	Protocol Amendments
28-Jun-2007	General Correspondence
29-Jun-2007	Information Amendments
02-Jul-2007	Safety Reports

05-Jul-2007	Protocol Amendments
06-Jul-2007	Safety Reports
10-Jul-2007	Safety Reports
12-Jul-2007	Safety Reports
13-Jul-2007	Safety Reports
17-Jul-2007	Safety Reports
23-Jul-2007	Safety Reports
30-Jul-2007	Protocol Amendments
30-Jul-2007	Safety Reports
03-Aug-2007	Safety Reports
06-Aug-2007	General Correspondence
10-Aug-2007	Safety Reports
10-Aug-2007	Information Amendments
13-Aug-2007	Safety Reports
14-Aug-2007	General Correspondence
14-Aug-2007	General Correspondence
21-Aug-2007	General Correspondence
22-Aug-2007	Protocol Amendments
22-Aug-2007	Safety Reports

23-Aug-2007	Safety Reports
29-Aug-2007	Safety Reports
30-Aug-2007	Protocol Amendments
31-Aug-2007	General Correspondence
31-Aug-2007	Safety Reports
05-Sep-2007	Safety Reports
06-Sep-2007	Information Amendments
07-Sep-2007	General Correspondence
11-Sep-2007	General Correspondence
12-Sep-2007	Protocol Amendments
13-Sep-2007	Safety Reports
14-Sep-2007	Protocol Amendments
17-Sep-2007	Information Amendments
18-Sep-2007	Safety Reports
21-Sep-2007	Information Amendments
21-Sep-2007	General Correspondence
26-Sep-2007	Safety Reports
27-Sep-2007	Annual Reports
01-Oct-2007	Safety Reports

09-Oct-2007	General Correspondence
10-Oct-2007	Safety Reports
12-Oct-2007	Safety Reports
18-Oct-2007	Safety Reports
19-Oct-2007	General Correspondence
24-Oct-2007	Safety Reports
31-Oct-2007	Safety Reports
01-Nov-2007	General Correspondence
05-Nov-2007	General Correspondence
14-Nov-2007	General Correspondence
15-Nov-2007	Safety Reports
16-Nov-2007	Safety Reports
19-Nov-2007	**Original BLA Submission**
19-Nov-2007	Protocol Amendments
28-Nov-2007	Safety Reports
28-Nov-2007	Protocol Amendments
29-Nov-2007	General Correspondence
29-Nov-2007	Safety Reports
30-Nov-2007	General Correspondence

03-Dec-2007	General Correspondence
03-Dec-2007	Safety Reports
05-Dec-2007	General Correspondence
06-Dec-2007	Safety Reports
13-Dec-2007	General Correspondence
13-Dec-2007	Safety Reports
14-Dec-2007	Information Amendments
14-Dec-2007	Annual Reports
17-Dec-2007	General Correspondence
18-Dec-2007	Safety Reports
18-Dec-2007	Protocol Amendments
18-Dec-2007	General Correspondence
19-Dec-2007	General Correspondence
20-Dec-2007	General Correspondence
20-Dec-2007	Safety Reports
21-Dec-2007	General Correspondence
21-Dec-2007	Safety Reports
27-Dec-2007	Safety Reports
28-Dec-2007	Safety Reports

02-Jan-2008	Safety Reports
03-Jan-2008	General Correspondence
04-Jan-2008	General Correspondence
04-Jan-2008	Safety Reports
07-Jan-2008	Safety Reports
09-Jan-2008	Safety Reports
10-Jan-2008	General Correspondence
11-Jan-2008	Protocol Amendments
11-Jan-2008	General Correspondence
14-Jan-2008	Information Amendments
16-Jan-2008	Safety Reports
18-Jan-2008	General Correspondence
22-Jan-2008	Safety Reports
22-Jan-2008	Protocol Amendments
22-Jan-2008	General Correspondence
23-Jan-2008	General Correspondence
25-Jan-2008	Information Amendments
28-Jan-2008	Safety Reports
31-Jan-2008	General Correspondence

01-Feb-2008	General Correspondence
01-Feb-2008	Safety Reports
04-Feb-2008	Safety Reports
05-Feb-2008	Safety Reports
07-Feb-2008	General Correspondence
08-Feb-2008	Safety Reports
11-Feb-2008	Safety Reports
13-Feb-2008	Safety Reports
13-Feb-2008	General Correspondence
18-Feb-2008	Safety Reports
18-Feb-2008	General Correspondence
19-Feb-2008	General Correspondence
20-Feb-2008	General Correspondence
21-Feb-2008	Safety Reports
25-Feb-2008	Protocol Amendments
26-Feb-2008	Protocol Amendments
26-Feb-2008	Safety Reports
28-Feb-2008	General Correspondence
03-Mar-2008	Safety Reports

05-Mar-2008	Protocol Amendments Information Amendments
07-Mar-2008	General Correspondence
10-Mar-2008	Safety Reports
12-Mar-2008	General Correspondence
13-Mar-2008	General Correspondence
18-Mar-2008	Protocol Amendments
18-Mar-2008	General Correspondence
19-Mar-2008	General Correspondence
19-Mar-2008	Safety Reports
20-Mar-2008	General Correspondence
24-Mar-2008	General Correspondence
25-Mar-2008	General Correspondence
26-Mar-2008	Safety Reports
28-Mar-2008	Safety Reports
28-Mar-2008	General Correspondence
31-Mar-2008	General Correspondence
31-Mar-2008	Safety Reports
02-Apr-2008	General Correspondence
03-Apr-2008	General Correspondence

04-Apr-2008	Safety Reports
04-Apr-2008	General Correspondence
07-Apr-2008	General Correspondence
08-Apr-2008	General Correspondence
08-Apr-2008	Safety Reports
08-Apr-2008	General Correspondence
09-Apr-2008	Safety Reports
10-Apr-2008	General Correspondence
11-Apr-2008	General Correspondence
14-Apr-2008	Meeting Request
14-Apr-2008	General Correspondence
15-Apr-2008	Protocol Amendments
15-Apr-2008	Safety Reports
15-Apr-2008	General Correspondence
16-Apr-2008	Safety Reports
16-Apr-2008	General Correspondence
18-Apr-2008	General Correspondence
18-Apr-2008	Safety Reports
18-Apr-2008	General Correspondence

23-Apr-2008	Safety Reports
24-Apr-2008	General Correspondence
24-Apr-2008	Safety Reports
25-Apr-2008	General Correspondence
30-Apr-2008	General Correspondence
30-Apr-2008	Safety Reports
30-Apr-2008	Safety Reports
30-Apr-2008	General Correspondence
02-May-2008	Protocol Amendments
06-May-2008	Safety Reports
09-May-2008	General Correspondence
09-May-2008	Safety Reports
13-May-2008	General Correspondence
13-May-2008	Safety Reports
14-May-2008	Safety Reports
14-May-2008	General Correspondence
16-May-2008	Protocol Amendments
19-May-2008	Safety Reports
22-May-2008	Safety Reports

23-May-2008	General Correspondence
27-May-2008	Safety Reports
29-May-2008	General Correspondence
30-May-2008	General Correspondence
03-Jun-2008	Safety Reports
03-Jun-2008	General Correspondence
04-Jun-2008	General Correspondence
05-Jun-2008	General Correspondence
09-Jun-2008	Safety Reports
09-Jun-2008	General Correspondence
10-Jun-2008	Safety Reports
12-Jun-2008	General Correspondence
13-Jun-2008	Safety Reports
13-Jun-2008	General Correspondence
16-Jun-2008	General Correspondence
17-Jun-2008	Safety Reports
17-Jun-2008	General Correspondence
18-Jun-2008	Safety Reports
18-Jun-2008	General Correspondence

20-Jun-2008	General Correspondence
23-Jun-2008	Safety Reports
23-Jun-2008	General Correspondence
24-Jun-2008	Protocol Amendments
24-Jun-2008	Information Amendments
24-Jun-2008	Safety Reports
25-Jun-2008	General Correspondence
26-Jun-2008	General Correspondence
27-Jun-2008	General Correspondence
30-Jun-2008	General Correspondence
30-Jun-2008	Safety Reports
01-Jul-2008	General Correspondence
02-Jul-2008	Safety Reports
02-Jul-2008	General Correspondence
03-Jul-2008	General Correspondence
07-Jul-2008	Information Amendments
07-Jul-2008	General Correspondence
07-Jul-2008	Safety Reports
08-Jul-2008	General Correspondence

09-Jul-2008	Safety Reports
10-Jul-2008	Protocol Amendments
11-Jul-2008	General Correspondence
11-Jul-2008	Safety Reports
11-Jul-2008	Information Amendments
14-Jul-2008	Information Amendments
14-Jul-2008	General Correspondence
14-Jul-2008	General Correspondence
15-Jul-2008	Information Amendments
15-Jul-2008	Safety Reports
15-Jul-2008	General Correspondence
16-Jul-2008	General Correspondence
17-Jul-2008	General Correspondence
18-Jul-2008	General Correspondence
21-Jul-2008	General Correspondence
22-Jul-2008	General Correspondence
23-Jul-2008	General Correspondence
23-Jul-2008	Safety Reports
24-Jul-2008	Safety Reports

24-Jul-2008	General Correspondence
25-Jul-2008	General Correspondence
28-Jul-2008	Information Amendments
30-Jul-2008	General Correspondence
30-Jul-2008	Safety Reports
01-Aug-2008	Safety Reports
01-Aug-2008	General Correspondence
03-Aug-2008	General Correspondence
06-Aug-2008	General Correspondence
06-Aug-2008	Safety Reports
07-Aug-2008	General Correspondence
08-Aug-2008	General Correspondence
08-Aug-2008	Safety Reports
11-Aug-2008	General Correspondence
13-Aug-2008	Safety Reports
14-Aug-2008	Safety Reports
14-Aug-2008	General Correspondence
15-Aug-2008	General Correspondence
18-Aug-2008	Information Amendments

18-Aug-2008	Safety Reports
18-Aug-2008	General Correspondence
19-Aug-2008	General Correspondence
21-Aug-2008	General Correspondence
22-Aug-2008	Protocol Amendments
22-Aug-2008	General Correspondence
25-Aug-2008	Safety Reports
26-Aug-2008	General Correspondence
27-Aug-2008	Safety Reports
28-Aug-2008	General Correspondence
29-Aug-2008	Safety Reports
29-Aug-2008	General Correspondence
02-Sep-2008	General Correspondence
02-Sep-2008	Safety Reports
03-Sep-2008	Safety Reports
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08-Sep-2008	General Correspondence

09-Sep-2008	Information Amendments
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09-Sep-2008	Safety Reports
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23-Sep-2008	Meeting Request
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04-Nov-2008	Safety Reports
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04-Mar-2009	Protocol Amendments
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02-Dec-2009	Safety Reports
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02-Jan-2010	General Correspondence
04-Jan-2010	Protocol Amendments
04-Jan-2010	Protocol Amendments
04-Jan-2010	Safety Reports

04-Jan-2010	General Correspondence
05-Jan-2010	Safety Reports
06-Jan-2010	Safety Reports
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07-Jan-2010	Safety Reports
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08-Jan-2010	**BLA Approval**